

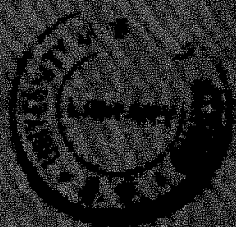
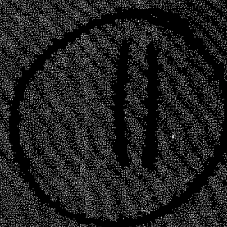
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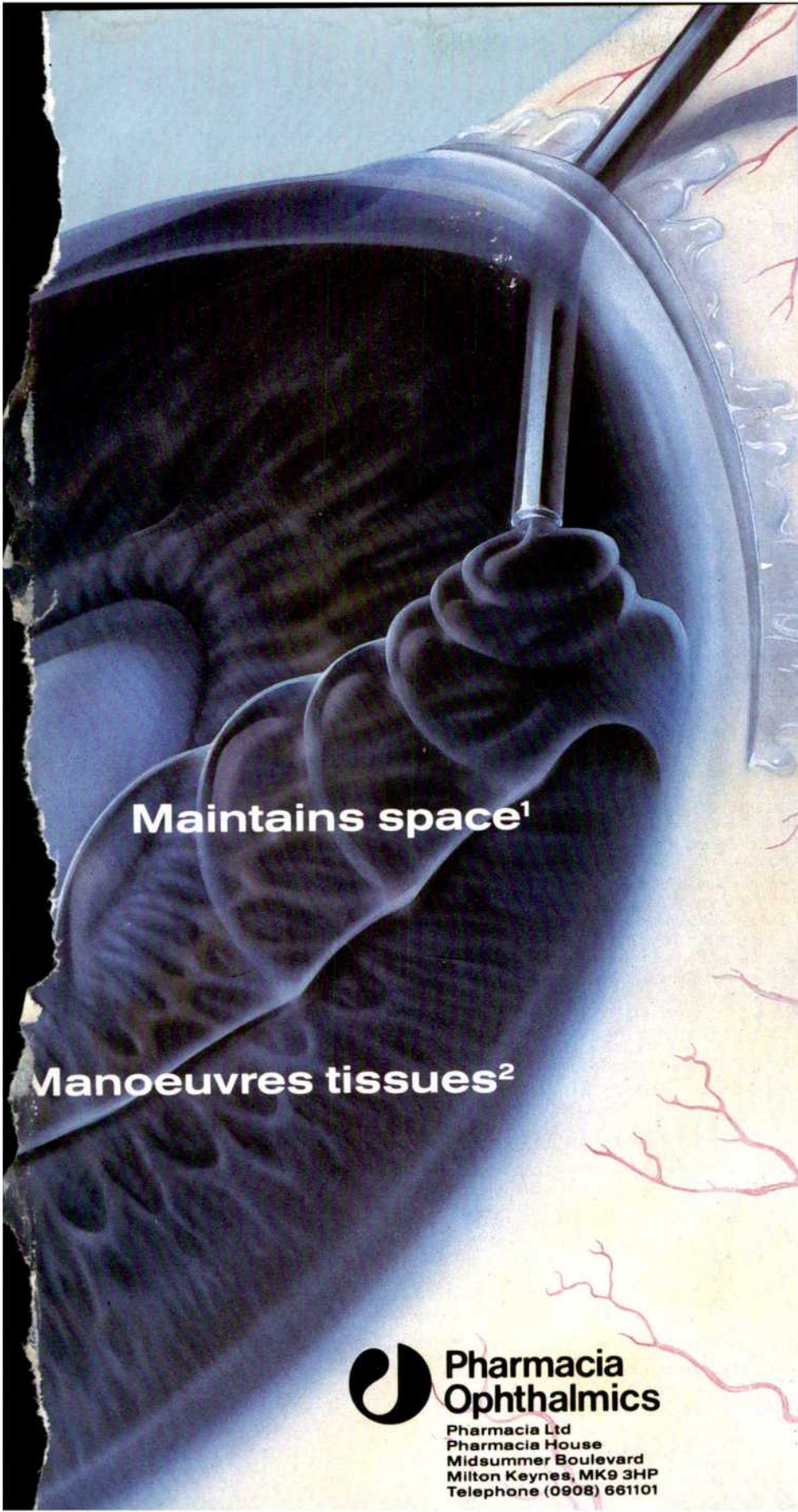
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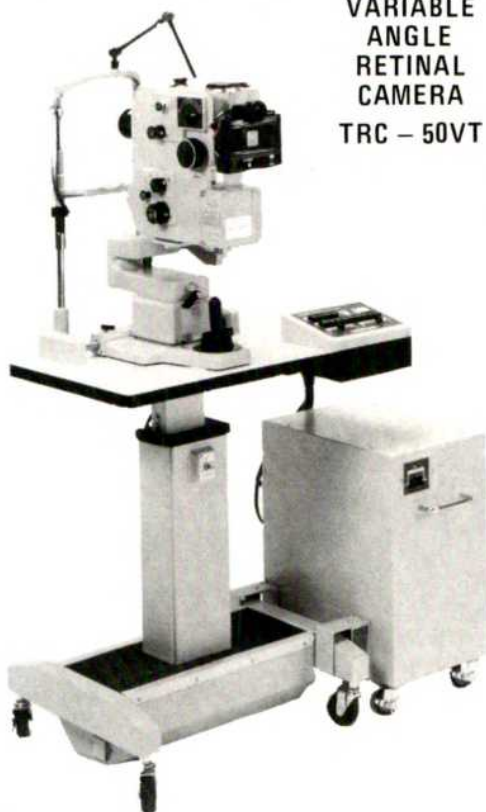
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1. Garner LL, et al, *Amer. J. Ophthalmol.* 1963 **55**, 323-327.
2. Duke Elder, WS, *Textbook of Ophthalmology* as quoted in: Moses, RA, *Adlers Physiology of the Eye*, 1975: **192**.

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Editorial: Retinal macroaneurysms

One of the tasks an Editor has to perform is to try to transform himself into somebody else, at least not just one other body but the whole collective consciousness of his readers, or to express it simply to put himself in their place. What do the readers like? What do they appreciate? What do they regard as new and exciting or old and boring?

Unfortunately a scientific journal quite often has to print material that is boring to some readers, but it must be remembered that all readers are not the same: long and involved descriptions of electro-diagnostic apparatus or immense charts of the exact details of the procedures carried out, the angles or prism degrees before and after together with interesting data such as the age of onset, degree of binocularity, and left or right handedness in 114 cases of squint may each have their fans, but you can be sure not everyone will find them interesting.

But from time to time an article comes in which the Editor feels, having made the transformation previously mentioned, will interest everyone. And what could be a more certain winner in this respect than a brand new cause of vitreous haemorrhage? At this point there are readers excitedly crying, 'But he's wrong, it's not new—all retinal experts know macroaneurysms cause vitreous haemorrhage.' To which the Editor will reply, 'Maybe they do know, but I

didn't and I would bet that the majority of my readers didn't either.'

Vitreous haemorrhage used to be taught as being due rather vaguely to hypertension or diabetes. However, during the 1950s we gradually became aware of the probable mechanisms involved, particularly of the role of neovascularisation in response to retinal ischaemia. During the same period the likelihood of some vitreous haemorrhages being due to tears in the retina also became recognised. Thus the principal causes of vitreous haemorrhages could be condensed into neovascularisation or direct retinal tearing, and these would cover most cases.

Thus it is exciting to have identified an entirely new cause with a specific mechanism to consider in our differential diagnosis, namely the rupture of a macroaneurysm, as reported this month by M N Abdel-Khalek and J Richardson. But does the aneurysm rupture or is the bleeding due to neovascularisation from associated vascular anomalies, as in diabetes mellitus or venous occlusion? The authors' 'presumed aneurysmal rupture' has a faint air of uncertainty about it and reminds us of the term 'presumed ocular histoplasmosis,' which actually means 'not ocular histoplasmosis.' Perhaps this is the next question which the authors will be able to answer for us.

RJHS

Retinal macroaneurysm: natural history and guidelines for treatment

M N ABDEL-KHALEK AND J RICHARDSON

From Sunderland Eye Infirmary, Sunderland

SUMMARY This report describes the features and clinical significance of retinal macroaneurysm. Two groups can be defined: those with acute aneurysmal decompensation, Group I; and those with chronic aneurysmal decompensation, Group II. Haemorrhage is the main feature of the former group and exudates of the latter. Systemic and local associations are noted, and guidelines for treatment by phototherapy are discussed.

Although the lesions have been observed since 1808,¹ Robertson² in 1973 first applied the term 'macroaneurysm' (MA) to retinal arterial lesions with the following characteristic features: (1) a saccular or fusiform ('blow-out' or 'cuffed') arterial swelling; (2) sited on the first three orders of the retinal arterial tree; (3) found mainly at arterial bifurcations (similar to aneurysms affecting the cerebral circulation).

Correspondence to Mr M N Abdel-Khalek, FRCSed, Eye Infirmary, Queen Alexandra Road, Sunderland SR2 9HP.

In this report we analyse a series of 19 patients with retinal MAs who were followed up for periods ranging from six months to 10 years. In general, symptoms arose from the sequelae of aneurysmal decompensation. Patients with acute aneurysmal decompensation had intraocular haemorrhage of varying degree (group I, Table 1) and those with chronic decompensation an exudative response (group II, Table 2).

Table 1 Group I: acute aneurysmal decompensation (haemorrhagic)

Case No.	Age	Sex	Type of haemorrhage	Site of MA	Association		Treatment	Visual acuity		Follow-up
					Ocular	Systemic		Onset	Final	
1	68	M	Intravitreal, intra-subretinal	LITA	None	Arteriosclerosis, angina	Xenon	CF	6/24	2 yrs
2	60	M	Pre-, intraretinal	LITA	None	Hypertension, COAD, Ca bronchus	None	6/60	6/9	2 yrs and 9/12
3	70	F	Intravitreal intra-subretinal	RITA	None	Hypertension (treated but uncontrolled)	Argon	PL	6/18	2 yrs
4	79	F	Pre-, intraretinal	LITA	Macular Drusen, SMD	None	None	6/9	6/12	1 yr and 3/12
5	70	F	R pre-, intraretinal	R STA	None	Rheumatoid arthritis	None	1/60	6/12	3 yrs and 4/12
6	63	F	Uncomplicated Intra-, subretinal	L STA	None	Idiopathic trigeminal neuralgia, asthma, hiatus hernia, diverticulitis	None	6/9	6/36	6/9
7	72	F	Pre-, intraretinal	L STA	None	Spondylitis	Argon	HMs	HMs	3 yrs and 2/12
8	75	F	Pre-, intraretinal, subretinal	R STA	L aphakia L retinal detachment	Hypertension (labile)	None	6/60	6/12	4/12

ITA=inferior temporal artery STA=superior temporal artery SMD=senile macular degeneration
COAD=chronic obstructive airways disease

Table 2 Group II: chronic aneurysmal decompensation (exudative)

Case No.	Age	Sex	Type of exudate	Site of MA	Association		Treatment	Visual acuity		Follow-up
					Ocular	Systemic		Onset	Final	
1	75	F	Perianeurysmal	L STA	None	Arteriosclerosis, stroke hypertension, arthritis	Clofibrate	6/18	6/18	4 yrs, died
2	70	F	Perianeurysmal	R STA	Old Choroiditis	Untreated pernicious anaemia	Xenon	6/12	6/12	17/12
3	77	F	Perianeurysmal	R STA	None	Angina	Clofibrate	6/24	6/9	18/12, died
4	69	F	Perianeurysmal	R STA	None	None	Xenon ×5	6/9	6/9	11 yrs
5	72	F	Perianeurysmal, macular oedema	R STA	None	Hypertension, stroke	Clofibrate	6/18	6/9	15/12, died
6	74	F	Perianeurysmal	L STA	SMD	Hypertension (untreated)	Xenon	6/18	6/18	6 yrs
7	60	M	Perianeurysmal, macular oedema	R STA	Bilateral chronic uveitis	Hypertension (untreated)	Argon	6/36	6/36	2 yrs and 6/12
8	52	F	Perianeurysmal	L STA	None	None	Argon ×2	6/9	6/9	2 yrs and 10/12
9	61	M	Macular exudates	R STA	Coats' disease	None	Xenon	6/24	6/60	1 yr
10	73	F	Perianeurysmal macular exudates	R STA	R STA A/V occlusion	Hypertension	Argon	6/60	6/60	2 yrs
11	73	M	Macular oedema and exudates	R STA	R STA A/V occlusion	Hypertension	None	6/12	6/6	5/12 died 3/12

STA=Superior temporal artery. ITA=inferior temporal artery. SNA=superior nasal artery. SMD=senile macular degeneration. A/V=arteriovenous.

Patients and methods

GROUP I: ACUTE ANEURYSMAL DECOMPENSATION

In this group intraocular haemorrhage of variable extent was encountered. When the haemorrhage was substantial we saw preretinal, subhyaloid or intravitreal bleeding. Less florid haemorrhage produced localised intraretinal bleeding.

GROUP II: CHRONIC ANEURYSMAL DECOMPENSATION

In this group prolonged abnormal leakage of plasma constituents across the aneurysmal wall led to the accumulation of yellow perianeurysmal intraretinal exudates with or without related macular exudate. A few showed macular exudate only. In cases with abundant circumaneurysmal exudate a high rate of transmural leakage seems likely. Scanty perianeurysmal exudate suggests a low leakage rate.

Of the 19 patients reviewed 17 had unilateral MAs and two had bilateral MAs.

METHODS

Ophthalmic examination included biomicroscopy, funduscopy, and intravenous fluorescein angiography repeated on various occasions during the follow-up period. In nine patients phototherapy (either xenon arc or argon laser) was used to achieve closure of the MA. Photocoagulation was applied initially in a circular perianeurysmal fashion, using

the lowest level of energy necessary to achieve grey-white retinal burns, and then direct to the aneurysm at the same intensity. Only in two cases was it necessary to repeat the treatment. Treatment was

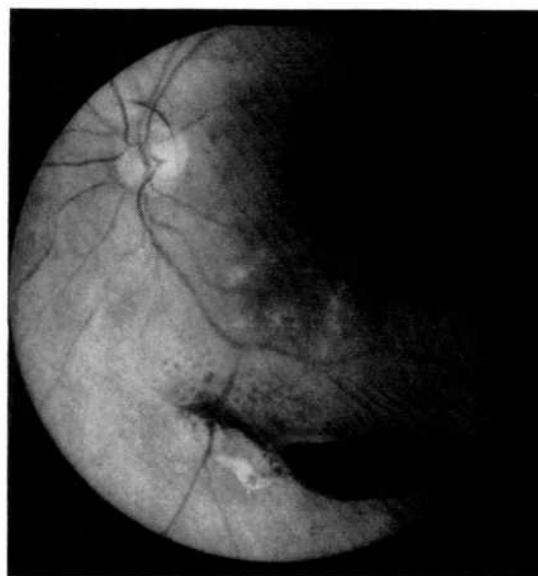
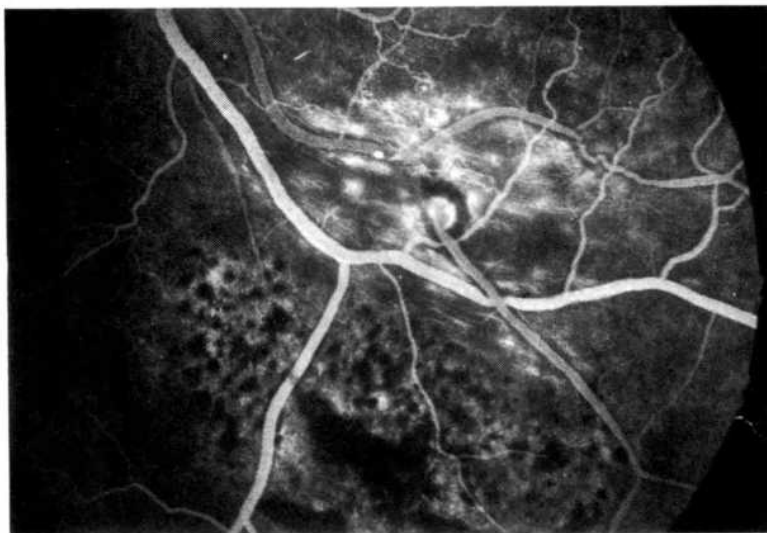


Fig. 1 Preretinal haemorrhage being absorbed, revealing an MA with surrounding exudate. Below that there are pigment clumping and subretinal scarring on the nasal side of the preretinal haemorrhage.

Fig. 2 Late-phase angiogram. The MA is of the blow-out type. The cap of perianeurysmal hypofluorescence is clear and may indicate mural thickening. This constant angiographic finding correlates well with the pale aneurysmal halo observed ophthalmoscopically.



given when macular function was threatened by progressive retinal exudation or by rebleeding.

Results

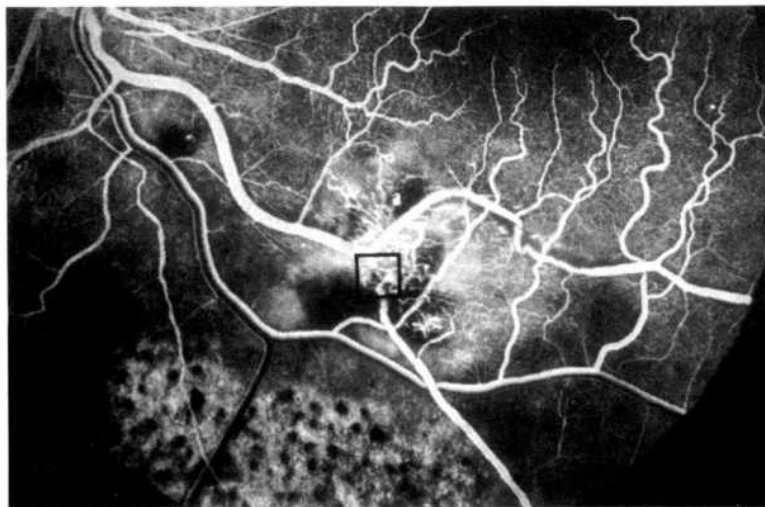
GROUP 1

Eight of our patients presented with sudden loss of vision due to haemorrhage from presumed aneurysmal rupture. The haemorrhage ranged in volume from a small, perianeurysmal, intraretinal bleed to a large combined vitreoretinal haemorrhage.

The sequence of events following aneurysmal rupture varied. Although the arterial perforation may close, leaving the aneurysm intact, the lesion remained haemodynamically unstable and was pre-

disposed to rebleed or allow transmission of tissue fluid across its walls (Fig. 1). Fluorescein angiography might then display the MA with associated vascular anomalies (Fig. 2). In this case aneurysmal closure is called for and can be achieved by direct phototherapy. Fig. 3 shows the angiographic appearance six months after one treatment with xenon arc phototherapy with closure of the MA and characteristic Z-shaped kink at the site of the former aneurysm. More commonly, Z-shaped kinks developed spontaneously after aneurysmal rupture and were apparently stable haemodynamically. They required no active therapeutic intervention. It is likely that many MAs rupture and close spontaneously and go unrecognised as the causative lesion

Fig. 3 In early venous phase the postcoagulative arterial stenosis at site of treatment is displayed. Perianeurysmal capillary meshwork remains showing attenuation. Vascular kink developing (square). Intravascular hyperfluorescent ring has disappeared, suggesting closure of endothelial defect.



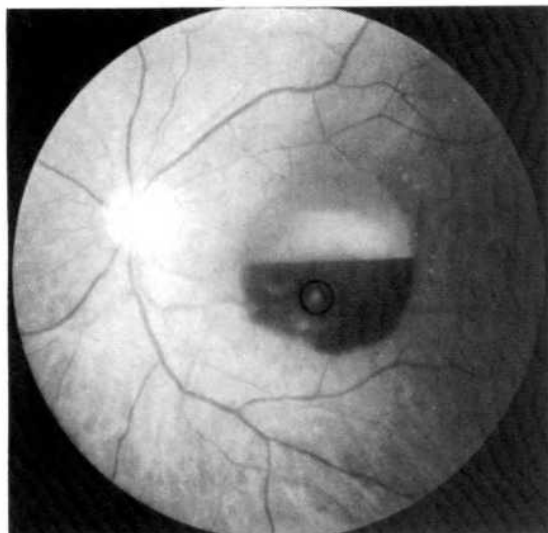


Fig. 4a Preretinal haemorrhage with a fluid level. The segment of the artery harbouring the MA is partly seen through the haemorrhage, and the site of the MA is just visible (circle).

in an episode of intraocular haemorrhage (Figs. 4a, b).

In three cases in which the haemorrhage was only preretinal the MA resolved untreated, with no significant ocular sequelae other than a pathognomonic Z-shaped kink on the offending arteriole marking the site of the former aneurysm. Cases that presented with intraretinal haemorrhage tended to develop a characteristic yellowish-grey saddle-shaped plaque centred on the site of the MA, with surrounding exudate. In such cases the arteriole bearing the MA

often went on to become heavily sheathed (Fig. 5). This saddle-shaped plaque is a characteristic post-haemorrhagic lesion and when seen later may cause diagnostic difficulty if the prior retinal haemorrhage was unrecognised.

Those MAs (three of eight group I cases) producing combined pre-, intra-, and subretinal haemorrhage may require phototherapy to halt posthaemorrhagic transmurular exudation or forestall further bleeding (Fig. 3).

GROUP II

Eleven cases presented with blurring of vision due to exudation from a retinal MA. Six of these had localised perianeurysmal exudates (Fig. 6), and three had in addition macular exudation. The remaining two had exudates distant from the MA (Fig. 7). Six group II patients had phototherapy to avert macular damage from intraretinal exudate and oedema. Closure of the MA was achieved in four cases by one treatment session only. The other two cases (4 and 8 in Table 2) had very large MAs which required more than one treatment session. Closure of the aneurysm was associated with kink formation and gradual exudate dispersal.

In five cases macular function was not threatened and phototherapy was unnecessary. Three of these were seen early in the series and were treated with clofibrate. Spontaneous closure occurred in one, while in the other two exudate formation never became severe.

Two patients had MAs associated with arteriovenous occlusions. In case 10 photocoagulation was planned, as the MA threatened macular function by generating profuse exudate, but the patient died before treatment could be carried out. In case 11

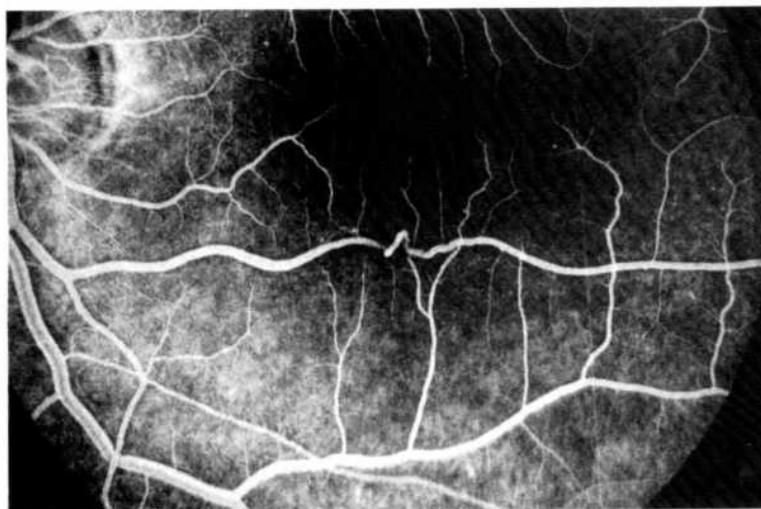
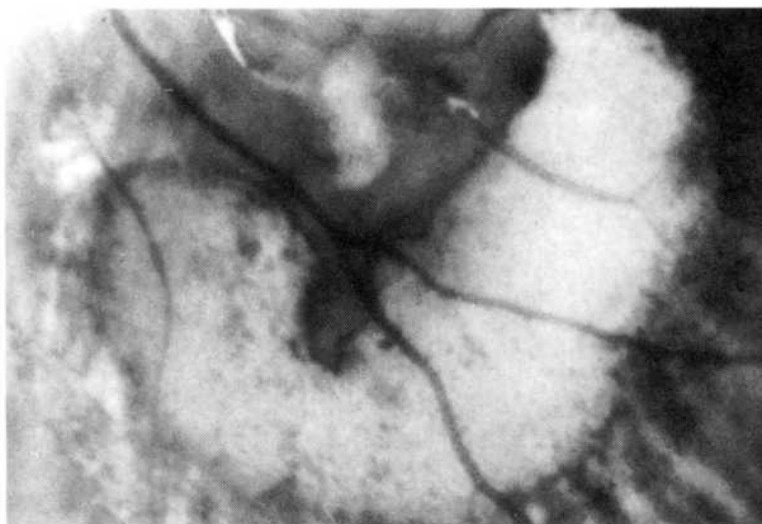


Fig. 4b Nineteen months after the haemorrhage, fluorescein angiogram showing Z-shaped kink at the site of the MA with attenuation of arterial calibre distal to it.

Fig. 5 Four months after haemorrhage, magnified photograph of the plaque. This shows scattered clumps of pigment resulting from intraretinal haemorrhage and a pigmentary border to the plaque from haemorrhagic disruption of the retinal pigment epithelium (RPE). Note marked arterial sheathing.



no significant aneurysmal leakage developed, and the vascular obstruction quickly became well compensated.

In our series retinal MAs occurred in 14 females and five males, showing a statistically very significant female predominance (approximately 3:1). They were unilateral in 90% and bilateral in 10%; single in 65% and multiple in 35% (Table 4). Aneurysms occurred on the superior temporal artery in 70% of the cases, on the inferior temporal artery in 35%, and on the superior nasal artery in 10%. None occurred on the inferior nasal artery. Each eye was affected with equal frequency (Table 4).

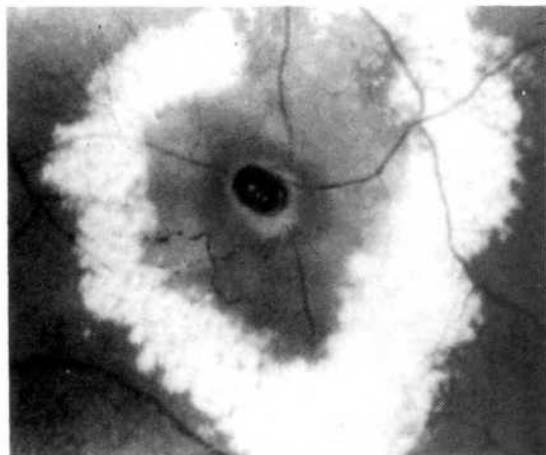


Fig. 6 Blow-out MA in a wide ring of retinal oedema encompassed by a solid ring of exudate. The perianeurysmal oedema is exaggerated by recent phototherapy between the MA and exudative ring.

Group I MAs were equally divided between superior and inferior temporal arteries. Group II MAs showed a definite predisposition towards the superior temporal artery as against the (10:3) inferior temporal artery (Table 5).

Retinal MAs mainly affect the older population (age range 56 to 73 years), most of whom suffer from hypertension as well as other systemic cardiovascular

Table 3 Systemic disease associated with retinal MA

No.	Systemic disease	%
9	Hypertension	45
6	Cardiovascular disease	30
2	Rheumatoid arthritis	10
1	Diabetes	5
1	Anaemia	5
1	Raised sedimentation rate	5

Table 4 Occurrence of retinal MA relating to sex, laterality, and number

	No.	%
Male	5	30
Female	14	70
Unilateral	17	90
Bilateral	2	10
Single	13	65
Multiple	6	35

Table 5 Site and distribution of retinal MA

	No.	%
Superior temporal artery	14	60
Inferior temporal artery	8	35
Superior nasal artery	1	5

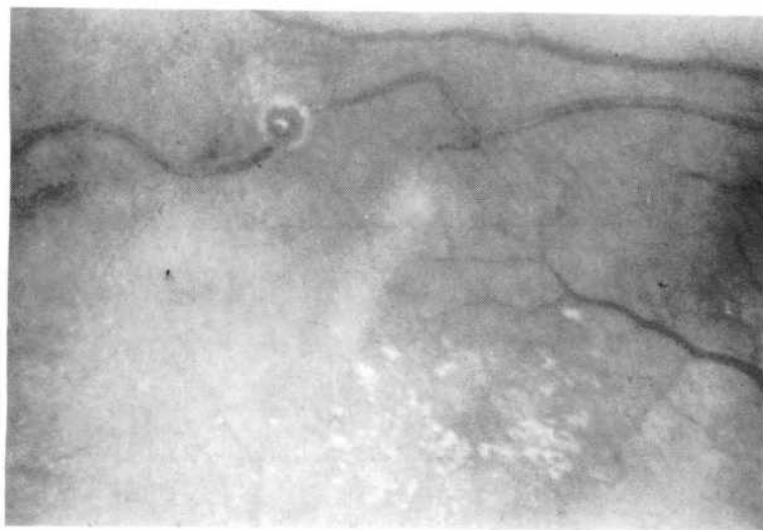


Fig. 7 In this case the haloed MA was not encompassed by exudates; these were seen only at a distance, near the macula.

disease.⁴⁵ Rheumatoid arthritis, diabetes, cerebrovascular disease and anaemia were also encountered (Table 3).

Discussion

Two classical types of aneurysm, saccular and fusiform, affect the retinal arteries. Fichte *et al.*³ preferred the terms 'blow-out' and 'cuffed'. The blow-out type in general was more prone to bleed (Fig. 8). Certainly this holds true for MAs on the first three orders of the retinal arterial tree, but large blow-outs on smaller arterioles may be exudative.

The haemorrhagic tendency of blow-out MAs may arise owing to the relatively easy perforation of a

thin, stretched aneurysmal sac, especially where the perfusion pressure is high, as in the first three orders of arterioles. The lower perfusion pressure in MAs on smaller vessels may predispose these lesions to exudation.

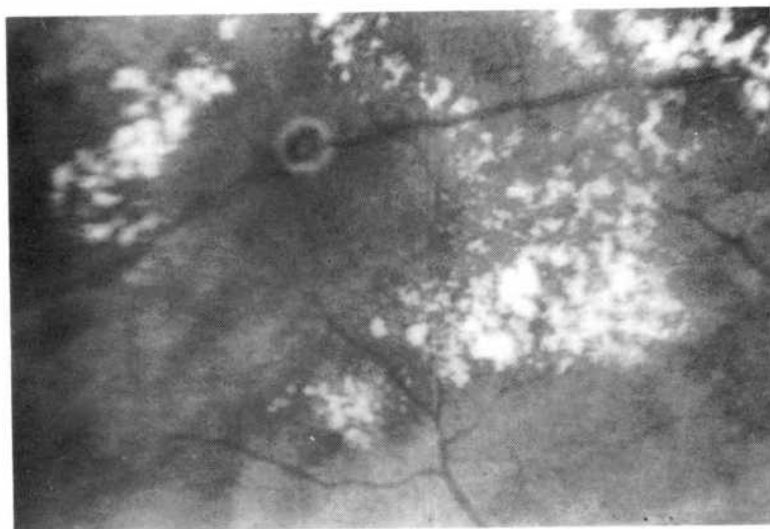
Group II MAs on the first three orders of the retinal tree tended to be of the fusiform (cuffed) variety. It is possible that this configuration encourages leakage of plasma derivatives but resists frank perforation (Fig. 9).

In group I MAs, where the haemorrhage is primarily preretinal, it is likely that the arterial rupture has occurred on the vitreal side of the MA. Posterior or posterolateral rupture of the aneurysm probably leads to intra- and subretinal haemorrhage.



Fig. 8 Eight months after haemorrhage shown in Fig. 1. Angiogram is arterial phase displaying MA adjacent to first bifurcation of inferior temporal artery (ITA). Note circumscribed circle of hyperfluorescence apparently within the arterial lumen just proximal to the second arterial bifurcation (circle). The latter may indicate endothelial damage as a precursor to arterial wall decompensation.²

Fig. 9 MA with halo, indicating gross thickening of the aneurysmal sac wall centred in a florid circinate ring of exudate extending remotely from the aneurysm to reach the macular area.



Large aneurysmal dehiscences produce haemorrhage at all levels (Fig. 10). Patients with acute haemorrhagic MAs have a better visual prognosis. Of the eight cases only one patient failed to regain useful central vision (Table 1, case 7). This patient was treated initially by perianeurysmal laser coagulation without any energy being applied directly to the MA. This seemed to close the MA, and no further treatment was given. She unfortunately bled from a



Fig. 10 Haemorrhage at all levels revealing an MA with surrounding exudate; below that there are pigment clumping and subretinal scarring on the nasal side of the preretinal haemorrhage.

second MA which formed distal to the original lesion on the superior temporal artery. This led to severe macular destruction and loss of central vision. Of the remaining seven patients (two requiring phototherapy) six regained central vision of 6/24 or better after being reduced to levels of acuity varying from perception of light to 6/36. One patient had a fall in vision by one line on the Snellen chart from 6/9 to 6/12 after a haemorrhage from a peripheral MA and subsequent degenerative macular changes.

Complete resorption of the haemorrhage occurred two to three months before the best visual acuity was achieved. A characteristic yellowish-grey plaque, akin to a disciform macular scar, subsequently developed at the site of intra- and subretinal bleeding (Figs. 1 and 5). The plaque is seen adjacent to the MA and is generally saddle-shaped, with the aneurysm in the saddle. Interestingly, the saddle was invariably inferior to the MA except in case 8 (Table 1), where the MA was sited on the superior temporal artery and the saddle was above the MA. If the plaque involved the macula (case 7, Table 1), central vision never recovered.

These plaques may evolve after a posterior aneurysmal rupture produces a dissecting haemorrhage and layer of blood superficial to the retinal pigment epithelium. The demarcation of this plaque-like scar with irregular pigmentation could then result from haemorrhagic penetration of the retinal pigment epithelium. The resultant scarring process is dissimilar from a disciform scar, because then there is neovascular penetration of Bruch's membrane.

In group II cases exudation was demonstrated by fluorescein angiography in the form of loss of vascular barrier to the dye, staining of the wall of the

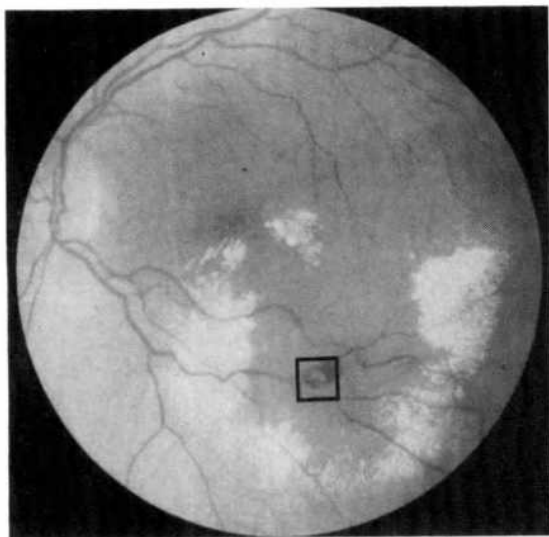


Fig. 11 A large blow-out MA within a venous bifurcation close to the main trunk of the ITA (square). Analysis of the fluorescein angiogram suggests the MA lies on a small radicle of the ITA. Encompassing the MA is a solid ring of exudate with intraretinal haemorrhage. Note bilobed dilation of ITA proximal to the origin of the feeder radicle to the MA.

aneurysm, and late leakage of the dye into the retina. In addition there is dilation and leakage from the capillary bed surrounding the dilated segment of the arteriole.

The occurrence of exudates at the macular area away from the offending vessel is not unique to retinal MA, as it occurs in other retinal vascular anomalies such as Coats' disease, Leber's miliary aneurysms, and von Hippel-Lindau diseases.

Exudates affecting the macular region, secondary to MA, occurred even when the MA was not in proximity to the macula, and we found that these cases had the worst prognosis whether treated or not (Fig. 11). Perianeurysmal exudates alone did not affect vision unless they extended to the macula. The distal circinate ring, in general, had a favourable prognosis and was absorbed if the aneurysm was treated.

In the group II cases three of 11 showed improvement in visual acuity ranging between two and three lines of the Snellen chart. The remaining eight showed no deterioration of their visual acuity. Six of these received phototherapy—three with xenon arc alone, one with argon laser alone, and two with xenon and argon.

Other signs were noted by previous workers,^{2,8} namely, kinking at the site of the resolved MA, arteriolar constriction proximal to the MA, and arterial sheathing distal to the MA. These changes

were also noted in our series. Postaneurysmal arterial closure is rarely seen, but arterial stenosis and sheathing are common findings. Post haemorrhagic sheathing of the parent vessel was commonly encountered, as was extreme variation in the calibre of arteries harbouring MA. The kinked appearance at the site of the resolved MA may result from fibrotic changes in the media of the arterial wall causing traction on the adventitial portion in that segment, leading to shortening of the artery. Counterforces between the fibrous contracture and the tensile strength of the adventitial attachments to the internal limiting membrane of the retina will lead to the appearance of the Z-shaped kink (Fig. 3). The same appearance was seen in MAs which were directly photocoagulated, presumably due to a similar mechanism, though no arterial perforation or bleeding occurred.

RESPONSE TO PHOTOTHERAPY

No immediate or late complications of photocoagulation were noted. In particular there was no case of bleeding either at the time of treatment or subsequently.

Nine patients (three of eight group I and six of 11 group II) were treated with phototherapy; one of these patients had bilateral MAs and accordingly 10 eyes received treatment. Argon laser was used in five patients, one receiving treatment to both eyes. Five patients had xenon coagulation, one patient being treated with both xenon and argon. In all cases but one phototherapy direct to the MA was given, the exception being case 7, group I.

In the last case the aneurysm subsided after preliminary perianeurysmal phototherapy, but it is worth noting that this patient developed a further aneurysm distal to the first along the same artery, with subsequent loss of central vision due to severe haemorrhage from the second aneurysm. The question remains whether direct phototherapy to the first MA may have forestalled the formation of the second aneurysm. In the remaining nine eyes the MA was directly treated in the first instance except in two cases where the MA was particularly large, and preliminary perianeurysmal treatment was thought to be necessary. In one case (case 4, group II) closure of the MA proved especially troublesome and in retrospect earlier phototherapy might have been advisable. No bleeding from direct photocoagulation of the MAs was encountered.

Of the 10 eyes treated two showed improvement in visual acuity (counting fingers to 6/24, perception of light to 6/18). These were cases presenting with vitreous haemorrhage in which the responsible MA was closed to forestall rebleeding or halt progressive exudation. Seven eyes showed no alteration in visual

acuity and were treated to prevent macular involvement in chronic MA-related exudation. One patient lost central vision from recurrent bleeding.

Of the remaining 11 eyes in the series eight were simply observed and three were treated with clofibrate. Five of the observed eyes presented with a ruptured MA (group I), all of which spontaneously formed a stable Z-shaped kink at the site of the former MA. Four of these recovered good central vision (6/60 to 6/9, 1/60 to 6/12, 6/36 to 6/9, 6/60 to 6/12), and a fifth lost a single line on the Snellen chart (6/9 to 6/12) due to the onset of degenerative changes at the macula. A sixth observed case (case 5, group I) had an asymptomatic MA in the contralateral eye. The remaining two observed eyes contained MAs secondary to arteriovenous occlusions. One of these achieved recovery of macular function (6/12 to 6/6) after a collateral circulation to the vascular obstruction had been established. The other (case 10, Table 2) had significant macular oedema and exudate and was awaiting phototherapy when she died.

Three group II eyes were treated with clofibrate. Two improved (6/24 to 6/9, 6/18 to 6/9), the latter (case 5, Table 2) with closure of the aneurysm and complete clearing of the exudate, the former with diminution of the exudate (case 3, Table 2). In the other case (case 1, Table 2) vision was unchanged and there was no increase in the volume of exudate. These three cases were seen early in our series and if seen later would simply have been observed and subjected to coagulation only if indicated.

Our indications for advising photocoagulation in retinal MA now are as follows:

(1) Recurrent bleeding or the threat of such. MA presenting only with haemorrhage should be observed initially and treatment offered only if decompensation of the MA continues without stable aneurysmal closure. Resolved MAs require no treatment.

(2) Exudates involving the macular area, since no time limit is known for the development of permanent damage to central visual function. Lewis *et al.*⁷ reported that direct treatment of MAs accelerated the rate of absorption of exudates with speedy recovery of visual function. It seems necessary to seal the MA directly to bring about immediate reduction in formation of exudates. As long as the MA is perfused exudates will continue to form, and we consider that direct phototherapy is a safe method of stemming aneurysmal leakage quickly and inducing closure of the MA.

CONCLUSION

Retinal MAs are probably commoner than is realised. They may confront the ophthalmologist in one of three ways: (1) sudden loss of vision due to

haemorrhage (group I); (2) minor visual disturbances reflecting an exudative response (group II); (3) symptomless—either with exudates where there is no direct or indirect macular involvement or as a resolved MA in the form of a Z-shaped kink with or without plaque.

Retinal MAs arise on the first three orders of the retinal arterial tree in most cases, though occasionally they may originate on small branches of the major arterial tree. The latter tend to reach a very large size and promote severe exudative phenomena in the retina.

'Slow to clear' vitreous haemorrhage may hide a ruptured aneurysm. When the haemorrhage clears, the only sign of a previously ruptured MA may be a vessel kink overlying a pseudodisciform lesion. In this way MAs as a cause of vitreous haemorrhage may go unrecognised. Where the MA is still visible when the haemorrhage resolves, treatment is indicated, as the risk of recurrent haemorrhage and/or exudation is high. A Z-shaped kink indicates a resolved and stable MA and does not require treatment. Treatment should also be given when macular function is threatened by leakage and exudation from the weakened wall of the MA and dilated surrounding capillaries.

We favour phototherapy direct to the MA either with xenon arc or laser, and we have observed no untoward sequelae. We have not encountered bleeding during or after treatment, as have others,^{1,4,8} though we accept that the risk of haemorrhage is probably greater with the argon laser. Direct treatment speeds the rate of absorption of perianeurysmal exudates and seals the MA itself. The question of direct or indirect treatment of MAs, however, remains controversial,^{1,4,8} and further study and follow-up are necessary.

We acknowledge with thanks the expert and industrious help of Mr Michael Strachan, medical photographer, and the following consultants who were kind enough to refer cases: Mr Claud Sharp, Mr David Allen, Mr R W Allchin, Mr Neil Manson.

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Prediction of amblyopia and squint by means of refraction at age 1 year

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SUMMARY In this series amblyopia, uncorrectable by spectacles and occlusion, was highly likely (48%) if a child had +3.50 or more dioptres of meridional hypermetropia at age 1 year. 45% of children with this refraction also had a squint. All those who remained with severely defective acuity in spite of treatment had either +3.50 or more dioptres of meridional hypermetropia or 4 or more dioptres of meridional myopia at age 1 year. These children were identifiable in the 3.7% of the population at age 1 year who showed high refractive errors. Squint as such was not so accurately predictable. Of those children with squint 71% had less than +3.50 dioptres of meridional hypermetropia at age 1 year—an incidence of 4.4% of the population. Apart from two 'congenital myopes' only 16% of these had residual amblyopia after treatment, and their last known acuity was never less than 6/12. Astigmatism in infancy or later is not significantly associated with squint or amblyopia.

In 1979 a pilot study¹ suggested that identification of hypermetropia at age 1 year should enable the prediction of most of the children who subsequently develop squint and/or amblyopia. This paper reports a more detailed study of a larger series of children who were refracted at age 1 year and re-examined at age 3½ or later. Analysis of the findings shows that prediction of amblyopia is more certain than the prediction of squint.

The youngest child in this sample is at present only 5 years old, and, although it is still possible for some of the children to present with abnormal, or normal, vision, the findings are presented now because they are complementary to the preliminary report on vision screening at 3½² and because it is unlikely that the overall conclusions will change significantly with time.

Material and methods

PATIENTS

The children were drawn from the same general practices reported in other publications.^{2,3} Fifteen of them received treatment with spectacles prescribed on the basis of their refraction at age 1 year as part of a separate investigation, the results of

which were reported in a recent paper.⁴ Since there is no evidence that this 'treatment' significantly alters their chances of having squint or amblyopia, reference to it has been omitted.

METHODS

Refraction was measured by retinoscopy at approximately 1 metre 30 minutes after instillation of cyclopentolate 1% drops. 1.75 D was subtracted from all the readings to allow for working distance and comparison with findings in other reports.^{1,3,5} The 'corrected' reading of the most hypermetropic meridian of a pair of eyes is recorded in Tables 1, 3, and 4 as the refraction unless the reading for any one meridian indicated 4 or more dioptres of myopia. Visual acuity was assessed only by a Linear Sheridan Gardiner or Snellen test at 6 metres.

Diagnosis of a visual defect is based on the last recorded observation, which may be at age 3½ or later. In this paper normal acuity is taken to be 6/12 or better in *both* eyes individually *and* no more than one line difference between a pair of eyes. A child whose acuity was defective without spectacle correction but normal with spectacles was classified as having correctable vision. On the other hand a child whose initial acuity with spectacles was defective or unknown and was not improved by occlusion to normal clearly had amblyopia. In between these were

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a number of children who initially had defective or unknown acuity with spectacles which subsequently became normal after occlusion. Amblyopia may have been eradicated by occlusion, but one cannot be sure

that some of them would not have become normal without occlusion. While many of these children may have been truly amblyopic, they have been recorded as having ?amblyopia.

Table 1 Meridional hypermetropia at age 1 year and visual outcome

Meridional hypermetropia	Normal vision	Correctable vision	Squint/ no amb	Squint/ doubtful amb.	Squint/ definite amb	Doubtful amb	Definite amb	% Of population screened
+4.00 or more	4	5	—	1	9	—	2	2.4
+3.50/+3.75	4	1	—	1	3	—	1	1.25
+3.00/+3.25	20	1	3	1	1	2	—	3.51
+2.50/+2.75	40	2	2	2	3	—	—	6.14
+2.00/+2.25	81	2	4	2	1	—	1	11.4
+1.75 or less	568	14	8	5	2	1	—	75.18

Table 2 Visual outcome of children who were myopic in one or more meridians at age 1 year

Myopia of most myopic meridian	Normal vision	Correctable vision	Squint/ no amb	Squint/ doubtful amb	Squint/ definite amb	Doubtful amb	Definite amb	Vision unknown	% of population screened
-0.25 to -3.75	126	7	3	2	—	2	—	3	17.1
-4.00 or more	—	1	—	—	2*	—	—	1	0.27

*First Child

Refraction at 1 year:
Last known acuity:

Right -4.25/+4.5
Right 6/35.

Left -2.75/+4.00
Left 6/6

Right exotropia. Occlusion declined

Second Child

Refraction at 1 year
Left exotropia and nystagmus

Right -8.75/+3.00
3 months' occlusion

Left -9.75/+4.00.
Last known acuity

Treated with spectacles from age 1 year
Right 6/9. Left 6/60.

Table 3A Prediction of squint

Meridional refraction at age 1 year	No squint	Esotropia	Exotropia
-4.00 D or more	—	—	2
-3.75 D—+3.25 D	733	27	5
+3.50 or more D	17	14	—

Table 3B Prediction of amblyopia

Meridional refraction at age 1 year	No amblyopia	Doubtful amblyopia	Definite amblyopia
-4.00 D or more	—	—	2
-3.75 D—+3.25 D	746	13*	6†
+3.50 or more	14	2*	15‡

*Twelve had normal acuity after occlusion; acuity of three unknown

†Two did not have occlusion

‡Two did not have occlusion.

Table 3C Prediction of amblyopia in children who had squint

Meridional refraction at age 1 year	No amblyopia	Doubtful amblyopia	Definite amblyopia
-4.00 D or more	—	—	2
-3.75 D—+3.25 D	17	10*	5†
+3.50 or more	—	2*	12‡

*Nine had normal acuity after occlusion; acuity of three unknown

†One did not have occlusion

‡Two did not have occlusion.

Results

The findings are summarised in Table 1 according to the amount of hypermetropia in the most hypermetropic meridian of a pair of eyes and the visual outcome. Some of the children had myopia in one or

more meridians at age 1 year, and the final visual acuity with glasses of these is shown in Table 2. Calculations based on these observations are shown in Tables 3 A, B, and C. The last known acuity of children treated with occlusion is shown in Table 4. Since almost all of the children were refracted at both 1 and 3½ years, it is possible to confirm the findings of others that astigmatism decreases and also to assess the possible role of infantile astigmatism in the aetiology of squint (Tables 5A and B).

The results of our pilot study¹ are confirmed, namely, that 2.5 D of meridional hypermetropia is highly significantly associated with squint and/or amblyopia (Table 6).

Table 4 Last known acuity in those children who had occlusion

Refraction at age 1 year	6/6	6/9	6/12	6/18	6/24	6/36	6/60
Myopia > -4.00 D	—	—	—	—	—	1	1
< +3.50 D	5	5	2	—	—	—	—
+3.50 or more D	1	4	3	3	1	—	4

Note: the seven children who had, after treatment, 6/24 or less acuity in one eye are all in that 3.7% of the population who had high refractive errors at age 1 year

Table 5A Astigmatism: number of children who had astigmatism at age 1 year and 3½

Amount of astigmatism in more astigmatic eye	Number of children at age	
	1 year	3½ years
<1.50	646	752
1.50—2.25	105	25
2.50—3.25	26	5
3.50 or more	9	4

This table summarises observations on the incidence of astigmatism. The refraction of 12 children at age 3½ was not known and these have been excluded.

Discussion

It is clear that as the level of meridional hypermetropia increased so did the incidence of both squint and amblyopia. If a theoretical cut-off level is raised from +2.50 D to +3.50 D it is evident that, apart from the two children who were highly myopic at age 1 year, 66% of those who had squint were not abnormally hypermetropic (+3.50 D or more) at age 1 year (Table 3A) (compare Fulton *et al.*⁶) and children who had <3.50 D hypermetropia at age 1 year had a 3.5% chance of having squint. Furthermore, when squint occurred in these children it was seldom associated with uncorrectable amblyopia. Indeed definite amblyopia was rare (0.8%). If, however, there was +3.50 D or more meridional hypermetropia at age 1 year, amblyopia was common (48%) and frequently associated with squint (Table 1). All the children who after occlusion and all other treatment still had the most severe amblyopia (6/24 or less) had either +3.50 or more D meridional hypermetropia or -4.00 D or more meridional myopia at age 1 year. These children usually present before age 3½, and since it seems that optical correction from age 1 year does not alter the prognosis⁴ these are the ones whose problem is primarily in need of further research. It should be noted that they can be found in only that 3.7% of the population who at age 1 year have these high refractive errors.

There were doubts about the wisdom of publishing a column of figures under the heading of doubtful

Table 5B Astigmatism: visual outcome of children who had more or less than 1.50 D astigmatism at age 1 year

	Astigmatism age 1 year	
	<1.50 D	1.50 or more
Normal/correctable vision	611	123
Squint, no amblyopia	13	4
Squint + amblyopia	20	9
Amblyopia	2	4
Total	646	140
Combined incidence of squint and/or amblyopia	5.11%	9.3%
Incidence of amblyopia only	3.4%	9.3%

This table relates astigmatism at age 1 year to squint and/or amblyopia.

Table 6 Association of 2.5 D of meridional hypermetropia with squint and/or amblyopia

	Normal or correctable vision	Squint/amblyopia	Total	% Abnormal
+2.5 or more	77	31	108	29%
<+2.5	665	24	689	3.2%
Total	742	55	797	

$$\chi^2=88.55, p<0.001$$

amblyopia, but the fact that we did not know for certain whether these children were truly amblyopic has to be admitted. If it is permissible to assume that occlusion eradicated amblyopia in those labelled as having doubtful amblyopia, two observations are suggested. Firstly (Table 3C), there may be two separate groups of children with convergent squint—one which consists of children with (usually) uncorrectable amblyopia (+3.50 D or more at age 1 year) and one of children with (probably) correctable amblyopia or no amblyopia at all (<+3.50 D at age 1 year). Secondly (Table 3B), there may be two sorts of amblyopia—one usually correctable and the other usually uncorrectable by occlusion, which can be differentiated by the amount of meridional hypermetropia in infancy. Alternatively, the efficacy of occlusion in restoring acuity to normal limits (as defined in this paper) may be related to the presence of more or less than +3.50 D of meridional hypermetropia at age 1 year (see also Table 4). Decisions on the time and duration of occlusion treatment had been taken before this observation was made.

AETIOLOGY OF AMBLYOPIA

Observations on this series of children raised a question about the aetiology of amblyopia. Eight of the 11 children who had <+3.50 D hypermetropia at age 1 year and subsequently had occlusion which 'normalised' their acuity had convergent squint, and

any initial amblyopia could have been secondary to the squint. There is no obvious explanation why they might have had form vision deprivation amblyopia. On the other hand 13 of the 15 children who had, at age 1 year, +3.50 or more D of hypermetropia remained definitely amblyopic after occlusion, and 10 of these had esotropia. Squint could have contributed to initial amblyopia, but what is the nature of their residual amblyopia? Was it primary or form vision deprivation amblyopia—wholly, partly, or not at all?

Detailed study of the refractions of the 31 children who had +3.50 or more D hypermetropia in the most hypermetropic meridian shows that in general the amblyopic group were more hypermetropic and had a larger amount of anisometropia than the non-amblyopic group. It is not possible, however, to state whether the differences were significant or whether at this level factor(s) other than refraction become important.

STRAIGHT-EYED AMBLYOPIA

Out of 38 children labelled as having possible or definite amblyopia only seven (18%) did not have squint. Much depends on the criteria for the clinical diagnosis of amblyopia, but it seems likely that the diagnosis of 'straight-eyed' amblyopia may have been made unnecessarily often in an earlier report.⁷

ASTIGMATISM

The relationship between astigmatism on the one

hand and squint and amblyopia on the other has never been defined. As others have shown, astigmatism is common in infancy, and the amount gradually decreased by age 3½. In this sample of children 1.50 or more D astigmatism in either or both eyes at age 1 year was not statistically significantly associated with squint, doubtful or definite amblyopia, or any combination of these.

We thank the general practitioners of Rushden and their health visitors for enabling us to study the children under their care. We also thank Mrs L A Neale and Mrs D Maddams for their secretarial help.

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Screening for visual defects in preschoolchildren

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SUMMARY There is no evidence to support the suggestion that a widespread programme of vision screening at age 3½ should be instituted. Some of the practical problems and defects of such a programme are outlined. If the issues raised are to be resolved by further research, identification of preschoolchildren who have visual problems will be facilitated by a screening procedure involving refraction and possibly a cover test.

In 1976 the Court Report¹ recommended that children should have their vision screened at the age of 3½ years. Screening at this age is supported on the grounds that squint and amblyopia would be identified at an age when remedial treatment might be successful. However, although a number of trials of screening children at this age have been conducted over the past 20 years,² screening has never been continued long enough for a full evaluation. The two most recent reports on this subject^{3,4} have not produced convincing evidence in favour of vision screening at this age.

While it is important that new advances should be introduced into medical practice, it would be wrong to adopt a procedure before it had been adequately evaluated. Sackett and Holland⁵ have pointed out that 'implementation of untested community screening or treatment renders their subsequent evaluation more difficult and less decisive . . . indeed it may become impossible to correct the original error.' As has been found for screening and treatment for cervical cancer, once a procedure has been introduced and accepted by both clinicians and the public, it is extremely difficult then to withdraw that service or even to subject it to a randomised controlled trial. Such a trial, therefore, should be carried out before a new screening procedure is introduced.

The investigation reported here, conducted in a circumscribed area of Northamptonshire, attempts to determine to what extent screening of 3½-year-old children for visual defects would satisfy the criteria outlined by Wilson and Jungner.⁶ It represents a preliminary report of the findings of six years of

screening children at this age and deals with the methods that are available to do this, the visual defects found, and with the follow-up and treatment offered on the detection of a possible defect. The children screened were born between January 1973 and December 1978, and conclusive information on the vision of some of the younger ones may yet present itself.

Earlier investigations were confirmed to assessment of visual acuity at the age of 3½.⁷ Two other methods have since been suggested: (1) a subjective test for stereoacuity⁸; (2) an objective search for abnormal refractions.⁹ The use of all three methods of identifying 'abnormal vision' is compared here.

For the purpose of this article 'abnormal vision' means squint and/or defective visual acuity. The heading 'defective visual acuity' includes both blurred vision correctable by spectacles alone and amblyopia. In our experience it has not been easy to differentiate between these two conditions in a preschool child. Although ophthalmologists and others profess to be primarily interested in early identification and treatment of amblyopia, defective visual acuity correctable by spectacles alone is just as important.

Patients and methods

SAMPLE

All children who were on the lists of three general medical practices in the towns of Rushden and Higham Ferrers were sent appointments for vision screening during the month they attained the age of 3½ years. Names were obtained from the health visitor's records and practice age/sex registers. The children were born between 1 January 1973 and 31 December 1978. Most of those born in the years

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1975-8 had also previously been sent appointments for vision screening at 1 year of age, and these particular children form the basis of an adjacent paper⁹ reporting the ability to predict amblyopia at age 1 year.

Those who did not attend for screening at 3½ were not sent a second appointment, but hospital records were searched to see if they had previously been identified as having a visual problem. A record was also kept of children seen after the age of 3½. This includes two groups of children: those who were thought to be normal at 3½ but who were subsequently found to have abnormal vision; and those who did not attend at 3½, some of whom were living in the district but were not known to the authorities.

The follow-up period varied, with those born in December 1978 being followed up to 5 years of age and those born in January 1973 to 11 years of age.

METHODS OF VISION SCREENING

All the children were seen first by an orthoptist, who: (1) performed the cover test; (2) recorded visual acuity using only the Linear Sheridan-Gardiner or Snellen test at 6 metres; and (3) recorded stereo-acuity using the Reinecke E test, but this was later abandoned. Cyclopentolate 1% drops were then instilled into both eyes, and 30 minutes later retinoscopy was performed, in all cases by the same ophthalmologist.

If a child did not have normal visual acuity or had a squint, the orthoptist gave the mother a note stating the defect found and instructed her not to show it to the ophthalmologist until he asked for it after retinoscopy had been performed. Thus clinical examination was performed in ignorance of the retinoscopy findings, and retinoscopy was carried out without prior knowledge of the visual acuity.

Vision was deemed to be abnormal if there was a squint and/or, at the time of screening, defective acuity without optical correction. Criteria for defec-

tive acuity were vision of 6/12 partly or less in either eye and/or a difference of more than one line between the acuities of a pair of eyes even if the acuity was better than 6/12. If acuity was defective and the cycloplegic refraction was 'normal' (see below), acuity was reassessed three to six months later without any treatment. Spectacles were prescribed if the refraction and vision were both 'abnormal' at the time of the first test.

A refraction (after 1% cyclopentolate) was considered to be abnormal if one or more of the following features were present: (1) bilateral spherical hypermetropia of +2.00 D sphere or more; (2) myopia; (3) astigmatism of 1.5 dioptres (myopic, hypermetropic or mixed), present in either or both eyes; (4) the refraction of one of a pair of eyes differed from its fellow by 1.00 or more D sphere and/or cyl.

Results

1507 children born during the years 1973-8 attended for vision screening as they reached the age of 3½. This represented a mean attendance rate of 72.3% of the target population and for individual years varied from 70.4% to 75.4%.

In the first year of the study 268 children were screened. It took an average of 4.1 minutes to assess the visual acuity of both eyes of a child, with a range of 2-11 minutes. The stereoacuity test took on average 1.6 minutes, with a range of 1-4 minutes. Retinoscopy was not timed, but since most children are emmetropic or nearly so it would on average have taken less than 1 minute per child.

Visual defects identified at the time of screening at 3½ years are only a proportion of the total since (Table 1): (1) 26% of those with abnormal vision had presented before 3½ years (col. 3); (2) 40.9% were identified at 3½ years screening (col. 4); (3) 33% presented after 3½ years (cols. 5 and 6). Of the latter

Table 1 Summary of when children presented with abnormal vision

Year of birth	Number (and percentage) with abnormal vision						
	(1) Population*	(2) Total with abnormal vision	% of population	(3) Presented before 3½ (%)	(4) Detected at 3½† (%)	(5) False/normal at 3½ (%)	(6) Not seen 3½ presented later (%)
1973	392	32	8.2	7 (21.9)	14 (43.4)	3 (9.4)	8 (25.0)
1974	389	29	7.5	8 (27.6)	6 (20.7)	7 (24.1)	8 (27.6)
1975	359	31	8.6	9 (29.0)	12 (38.7)	3 (9.7)	7 (22.6)
1976	415	28	6.7	8 (28.6)	11 (39.3)	3 (10.7)	6 (21.4)
1977	351	31	8.8	5 (16.1)	17 (54.8)	5 (16.1)	4 (12.9)
1978	364	30	8.2	10 (33.3)	14 (46.7)	5 (16.7)	1 (3.3)
Total	2270	181‡	8.0	47 (26.0)	74 (40.9)§	26 (14.4)	34 (18.8)

*All eligible children including non-attenders for screening at 3½ years at 3½ years †Includes 13 myopes ‡Includes 11 myopes

§Includes those where diagnosis of abnormal vision was uncertain

Table 2 Comparison of results of screening at 3½ years with last known vision status*

A. Screening by assessment of visual acuity and/or presence of squint Last known vision			
Vision at 3½	Normal	Abnormal	Total
Normal	1310	26	1336
Abnormal	30	61	91
Uncertain	67	13	80
Total	1407	100	1507

B. Refraction of children whose vision was uncertain at 3½
Last known vision

Refraction at 3½	Normal	Abnormal
Normal	56	5
Abnormal	11	8

C. Screening by cycloplegic refraction
Last known vision

Refraction at 3½	Normal	Abnormal	Total
Normal	1323	20	1343
Abnormal	84	80	164
Total	1407	100	1507

*Forty-one with normal refraction and uncertain vision were not followed up

children 43% apparently had normal vision at 3½ years, and they are therefore 'false negatives' of vision screening. The remaining 57% either did not attend at 3½ years or were not known to be living in the district at that time.

The results of screening for visual acuity plus a cover test are shown in Table 2A. Two-thirds of the 91 children who were recorded as having abnormal vision actually had a visual defect, but in the case of an almost equal number of children (80 or 5.3% of those who attended), the visual acuity was uncertain or could not be recorded. Refraction helped in the assessment of these children (Table 2B). There were 30 'false positives' of vision screening, but 24 of these had a normal refraction at 3½ years.

Table 5 Last known acuity of children born 1975–8 identified as having abnormal vision as a result of screening at 3½ and their refraction at age 1 year

Meridional refraction at age 1 year	Visual acuity						
	6/6	6/9	6/12	6/18	6/24	6/36	6/60
+3.50 D or more	1(1)	4(2)	2(1)	3(2)	1(1)	1	1(1)
<+3.50 D	15(1)	10(2)	1	1	—	—	—
Unknown	2	3	4(2)	1(1)	—	—	—

Figures in brackets indicate number of children who had occlusion

This table illustrates how knowledge of the refraction at age 1 year could help to predict eventual amblyopia after treatment. If a child had had <+3.50 D meridional hypermetropia at age 1 year, he/she had a much better chance of achieving normal acuity without occlusion than a child who had +3.50 or more D at 1 year would achieve even after occlusion

Table 3 Results of test for stereoacuity

Stereoacuity	Number of children	
	Normal vision	Abnormal vision
Normal	397	8
Abnormal	28	4
Impossible	94	4
Not recorded	16	8

Table 4 Results of treating those children identified as having defective vision at age 3½ or following uncertain vision at 3½

	Last known visual acuity									
	6/5	6/6	6/9	6/12	6/18	6/24	6/36	6/60	<6/60	
Spectacles only	4	21	13	4	4	—	1*	—	—	
Spectacles + occlusion	1	2	4	3	4	1	—	1	—	
No treatment	2	4	1	2	1	—	—	—	—	

*Occlusion declined

The results of screening by refraction alone are shown in Table 2C. Approximately half of those with an abnormal refraction had abnormal vision, but 20% of those with abnormal vision had a normal refraction. A squint should have been identified in most of these, but it is not always easy to be sure in practice if a small squint is present. The stereoacuity test proved too unreliable, and 22% of the children either would not attempt the test or obviously guessed (Table 3).

Children identified at 3½ years as having abnormal vision were followed up, and most received treatment. The last known acuities of these children are recorded in Table 4. Uncertainty about what an individual child's visual acuity really was made it difficult to decide whether a child of this age had amblyopia requiring occlusion, but when occlusion was given there was only a modest improvement in acuity (Fig. 1). Knowledge of the refraction at age 1 year helped to decide whether amblyopia was likely,

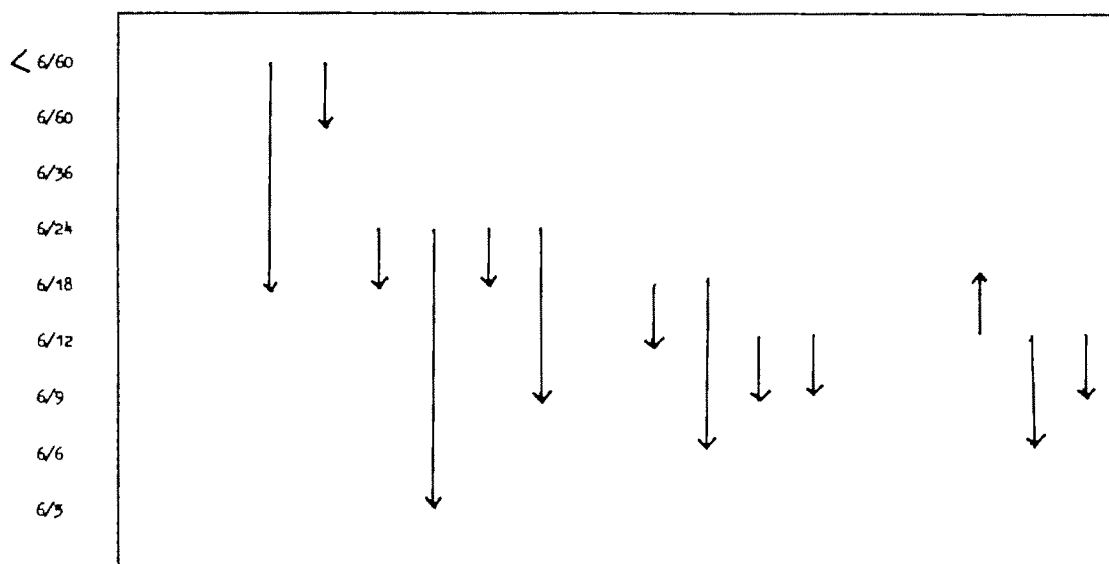


Fig.1 Effect of occlusion in individual children identified as having reduced acuity at age 3½. Arrows indicate the direction of change in acuity for each child from 3½ years of age to most recent testing.

and Table 5 shows that abnormal hypermetropia at age 1 year was more likely to be associated with genuinely defective acuity. There was a similar link with infantile hypermetropia in the case of children who presented (with squint) before the age of 3½ years (Table 6).

Table 7 shows, for all the children in the population sample identified as having abnormal vision, the last known level of acuity irrespective of whether treatment was given. It is important to note that nine of the 10 children left with a severe defect of acuity (6/60 or less) had presented before age 3½ years, that is, prior to screening.

Discussion

There has not yet been time for the final picture of the visual characteristics of these children, particularly

the younger ones born in 1978, to become clear. However, our experience so far prompts some comment on the problems and benefits of early screening at 3½ years. Screening at this age does detect a considerable proportion (41%) of children's visual defects, but it must be followed by additional case finding if all abnormalities are to be detected.

The test for stereoacuity proved to be impracticable for many children at this age, and we do not recommend its use for screening. Neither of the other two tests, namely, (1) for visual acuity and/or squint, or (2) for abnormal refractions, was perfect. The following observations are made on the assumption that the first of these methods is the one most likely to be used by non-medical personnel.

(1) Responses of individual children to the test of visual acuity were variable and often uncertain. Refraction proved helpful in distinguishing those

Table 6 Last known acuity of children born 1975–8 who presented before 3½ and their refraction at age 1 year

Merdional refraction at age 1 year	Visual acuity							?
	6/6	6/9	6/12	6/18	6/24	6/36	6/60	
+3.50 D or more or > -4.00 D	—	1(1)	2(2)	—	—	—	3(2)	—
<+3.50 D	7(2)	3(2)	3(3)	—	—	—	—	1
Unknown	2	3	2(2)	1(1)	—	1*(1)	1(1)	1

Figures in brackets indicate number of children who had occlusion.

*This child had +6.25 D at age 16 months. He has also had occlusion.

This table illustrates how the presence of ametropia at age 1 year altered the prognosis for treating children who presented before 3½ with abnormal vision (i.e., squint).

Table 7 Age of presentation of children identified as having visual defects and their last known acuity (irrespective of whether treatment was actually given)

	Visual acuity								
	6/5	6/6	6/9	6/12	6/18	6/24	6/36	6/60	Unknown
Before 3½	—	11	10	7	4	1	1	9	4
At age 3½*	7	27	18	9	9	1	1	1	1
After 3½†	2	17	23	5	5	—	1	—	7

*Includes those with uncertain vision at 3½ and who were subsequently treated.

†Includes false normals at 3½

This table shows that most of the children in the total population sample who ended up, after all treatment, with the worst vision had presented (with squint, to the hospital clinic) before 3½

with normal vision from those with abnormal vision requiring treatment.

(2) 33% of the children in this population sample who had a visual defect were 'missed' by screening at 3½. 14.4% of the total with visual defects gave a 'false normal' response to the test; the remainder did not attend for screening, some because they were not known to be living in the district at that time. This is an administrative problem which could to some extent be overcome.

(3) 26% of the total number of children with a visual defect had presented before age 3½ (Table 1). In this sample (Table 7) nine of the 10 children who ended up with 6/60 or less were in this group, and, so far as they were concerned, screening at age 3½ was irrelevant.

Consideration of the results of treating children identified as abnormal by a screening procedure is an essential part of the assessment of the value of that screening procedure. Variable responses to visual acuity tests at this age made it difficult to differentiate children with amblyopia requiring occlusion from others with 'blurred vision' due to uncorrected errors of refraction. Most of the children achieved normal corrected acuity (Table 4), but the outcome of occlusion at this age was not very encouraging, only three of 16 achieving 6/6 (Fig. 1). These indifferent results may reflect uncertainty about who should have had occlusion and for how long. We eventually realised that the prognosis for treatment depended to some extent on whether a child had abnormal hypermetropia (+3.50 D or more in any one meridian) at age 1 year. This is illustrated for the children born between 1975 and 1978 (Table 5). Those who had abnormal refractions at 1 year often did not get and retain normal acuity, even with occlusion.

It is worth noting that the majority of children who presented before 3½ (Table 6) also achieved reasonable acuity. Two-thirds of these were known to be not abnormally hypermetropic at age 1 year, but four of

the five who ended up with 6/36 vision or less were abnormally hypermetropic at 1 year. This suggests that whether or not a child ends up with severe amblyopia after all treatment may be primarily determined by whether or not he had abnormal hypermetropia or (rarely) myopia at 1 year, and that this may be more important than the age at which defective vision is identified.

Children with abnormal refractions likely to lead to severe amblyopia can be identified in 3.7% of the population at age 1 year,⁹ but unfortunately optical correction from that age does not alter the prognosis.¹⁰ If we are to tackle the problem of severe amblyopia, these are the children who primarily require our attention, but their problem has to be approached before age 3½.

The case for preschool screening at 3½ for amblyopia rests on whether those children with mildly defective acuity corrected with glasses at 3½ would develop irreversible amblyopia, or their condition deteriorate in some other way after that age if they had not been treated. It will be extremely difficult to prove this, since a large number of children would need to be screened to identify a relatively small number with clearly defined visual defects. Some of these would then have to be given immediate treatment and others delayed treatment. If such a study were to be mounted, we think that screening for abnormal refractions would provide the quickest means of identifying cases, perhaps with the use of one of the recently developed photographic methods.^{11,12}

CONCLUSIONS

The relatively small number of children reported here makes it difficult to establish conclusively that the incidence or severity of amblyopia is reduced by preschool screening at 3½ years of age, since the overall incidence in any population is comparatively small. However, amblyopia detected at this age cannot often be eliminated. Of all visual defects apart from puberty-onset myopia fewer than half were detected through screening at 3½, and most of the children who ended up with the worst acuity even after treatment had presented before 3½. Only 70–75% of the population available attended screening, suggesting that it would be administratively problematic to organise screening of a relatively non-captive population of this age. Screening at age 1 year, however, achieved a 10% higher response rate, and the use of refraction at this age may provide a better means of identifying those children likely to have the most severe amblyopia. This study emphasises the need for further critical assessment before any move is made to introduce screening of 3½-year-old children on a national basis.

We thank all the general practitioners in Kettering and Rushden for allowing us to use their premises for the purpose of screening and thus giving us the possibility of studying their patients. We thank all the appropriate health visitors who arranged the details of the screening in the first place. We also thank Mrs L A Neale and Mrs D Maddams for secretarial assistance throughout.

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A comparison of postoperative refractive results with and without intraocular lens power calculation

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SUMMARY Sixty-five patients underwent intracapsular cataract extraction with implantation of Binkhorst iris-clip intraocular lenses (IOLs). For 31 patients the IOL was of a standard power. Thirty-four patients had axial length measurement and keratometry preoperatively, and IOLs calculated to produce emmetropia or 1 dioptre of myopia were implanted. There was no significant difference in the range of postoperative refractive results between the two groups.

The insertion of an intraocular lens (IOL) after cataract extraction has become widespread practice. When surgeons have mastered the basic techniques, they naturally attempt various refinements. One of these is the measurement of the eye preoperatively so that a lens of appropriate dioptric power may be inserted.

Since Binkhorst's¹ and Colenbrander's² descriptions of a method of calculating IOL power to minimise aniseikonia, many workers have tailored IOL power by measuring corneal curvature and the axial length of the eye, and reported their postoperative results. However, few surgeons have compared the refractive results of a group of patients whose IOL powers had been calculated with a group receiving IOLs of standard power. We report such a series.

Patients and methods

Sixty-five patients underwent intracapsular cataract extraction and insertion of a Binkhorst iris-clip intraocular lens by a single surgeon (VMR) using a standard procedure. After general anaesthesia five virgin silk sutures were placed in a corneoscleral incision. The cataract was removed with a cryoprobe, and a single 10/0 nylon iris suture placed to anchor the upper loop of the intraocular lens.

One group of 31 patients (32 eyes) received a standard power IOL of .19 dioptres in air, ± 0.5 dioptre depending on availability. This group com-

prised 21 women and 10 men, with a mean age of 68.9 years (range 50–86 years).

The second group of 34 patients (35 eyes) underwent preoperative ultrasonic measurement of the axial length of the eye with a Radionics Echo-Oculometer 3000. This system uses an applanation-type transducer. The corneal curvature of each eye was measured with a Haag-Streit keratometer. Using the Binkhorst formula, a Texas Instruments 58C/59 programmable calculator worked out the IOL powers required to produce emmetropia, and 1 dioptre of myopia, in each eye. Of these the lens with the power nearer to the standard ± 19 D in air was selected for implantation. Fourteen patients received lenses designed to produce emmetropia, and 20 patients (21 eyes) received lenses calculated to produce one dioptre of myopia.

The 'measured' group comprised 26 women and 8 men, of mean age 68.8 years (range 57–86 years). The patients were allocated to either group by the surgeon on a random basis, but no formal randomisation procedure was followed. One patient was excluded because axial length measurement revealed high myopia.

All patients underwent refraction six to 12 weeks after surgery and were prescribed glasses if necessary. Two patients (one 'measured' and one 'unmeasured') were not included in the series because their IOLs were removed soon after cataract surgery. One developed intractable pupil block glaucoma and one corneal decompensation.

The postoperative spherical equivalent refraction was calculated for each patient. In the unmeasured

group the difference between this and emmetropia was determined. In the measured group the difference between the postoperative refraction and the predicted refraction was determined.

Results

The powers of the intraocular lenses implanted in the measured group ranged from 16.5 to 24 dioptres in air. Fig. 1 shows the distribution of powers.

Visual acuity. Table 1 shows that the visual outcome for the two groups was similar. One patient in the unmeasured group had persistent cystoid macular oedema, but her corrected visual acuity remained at 6/12.

Refractive error. Postoperative astigmatism was similar in the two groups; mean 1.9 D (range 0.4 D, SD 0.9 D) in the unmeasured group, mean 1.97 D (range 0.6 D, SD 1.1 D) in the measured group.

Fig. 2 and 3 show the distribution of the difference between the spherical equivalent refraction and emmetropia for the unmeasured group, and between

Table 1 Postoperative corrected visual acuity

Corrected vision	Measured group	Unmeasured group
6/5	3	7
6/6	17	16
6/9	7	7
6/12	8	2

the spherical equivalent and predicted refraction for the measured group. In the unmeasured group 65.6% of the patients fell within 1 D of emmetropia, 90.6% fell within 2 D, and 100% within 3 D. In the measured group 74.3% of the patients fell within 1 D of the predicted refraction, 91.4% within 2 D, and 100% within 3 D.

A Mann-Whitney test showed that there was no significant difference between the groups ($p=0.8$). If the difference between spherical equivalent refraction and emmetropia is taken for both groups, there is still no significant difference between the groups (Mann-Whitney test $p=0.2$).

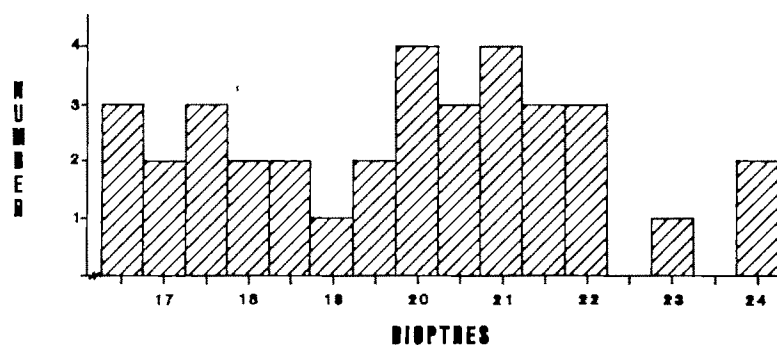


Fig. 1 Range of lenses implanted into measured group.

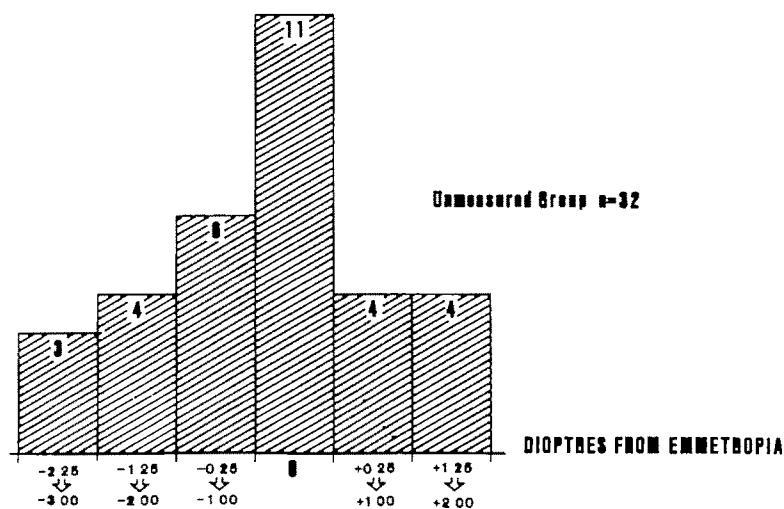
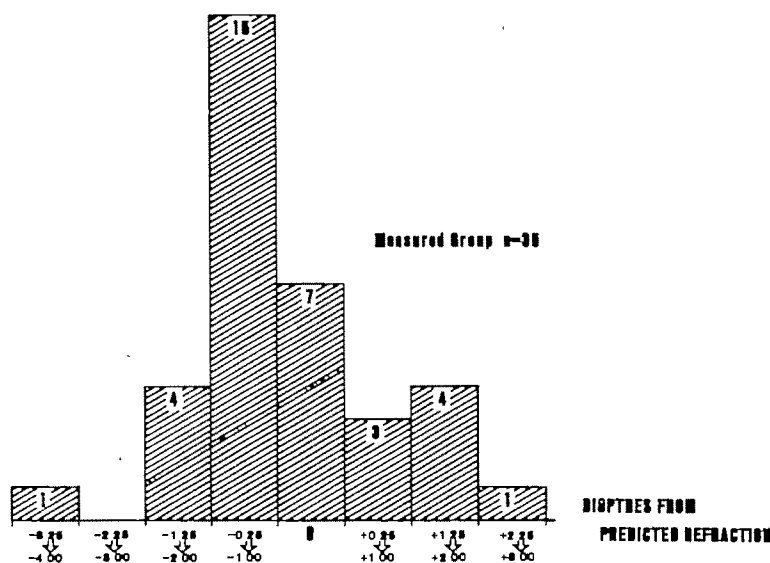


Fig. 2 Difference between postoperative refraction and emmetropia.

Fig. 3 Difference between postoperative and predicted refraction.



Discussion

Many workers have shown that the preoperative calculation of appropriate IOL power by measuring the corneal curvature and axial length is accurate and useful.³ In this series the accuracy of IOL measurements is similar to that of many reported series.⁴

The four main reasons why IOL calculations may be carried out are: (1) as a routine to achieve a desired postoperative refraction, usually emmetropia^{3,4}; (2) to minimise anisometropia in patients with a high refractive error in the fellow non-cataractous eye⁹; (3) as a routine to avoid unexpected high ametropia; (4) to avoid aniseikonia.¹⁰

In practice the fourth application does not seem to be widely used, but Hillman has shown that lens calculation is useful for planned ametropia in patients with a high refractive error in the fellow eye.⁹ However, a case has been made for routine preoperative lens calculation in all patients to achieve a desired refraction and avoid unexpected high ametropia.¹¹

The results of our series suggest that the use of a standard power IOL produces results as satisfactory overall as the routine calculation of IOL power. Where medical and technical resources are finite, routine lens calculation may not be indicated.

This study may be criticised on two main points. It is possible that a larger series would reveal more of a difference between the groups or some unexpectedly high refractive error in the uncalculated group.

In Hillman's series⁹ 100 consecutive patients received standard power IOLs and 100 received calculated IOLs. The difference between postopera-

tive spherical equivalent refraction and emmetropia were calculated. A Mann-Whitney test applied to these data shows a significant difference between the groups ($p=0.02$). However, the estimated difference of the means for these two groups was only 0.54 dioptre. This indicates that the statistical significance of the difference may be more than the clinical significance. Perhaps of more importance was the occurrence of several unexpectedly high post-operative refractive errors in the uncalculated group. For this reason we are doing a further study in which IOL power will be calculated if clinically indicated (see Percival¹¹) to avoid high ametropia.

The selection of patients for the present series was not truly random. Any unconscious selection bias would be expected to place ametropic patients in the measured group. This would reduce the difference in postoperative results between the two groups. In our study in progress half the patients without clinical indications for measuring will in fact have calculated IOLs and selection will be on a random basis.

Our thanks go to Dr Kent Woods for statistical help, Evelyn Dawes for typing the manuscript, and Alistair Rose and Mavis Rooney for preparing the illustrations.

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Elevating the hypotropic globe

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SUMMARY Twelve consecutive cases are reviewed of unilateral hypotropia due to various causes. In most of them the presenting complaint was of ipsilateral blepharoptosis. Some patients had undergone previous ineffective surgery. The surgical techniques employed and the results obtained are discussed, with emphasis on the necessity to test for inferior rectus restriction. Some interesting sensory results are also noted.

The combination of unilateral congenital ptosis with hypotropia of the ipsilateral eye is common.¹ Hypotropia may also accompany the Marcus Gunn jaw-winking syndrome and buphthalmos secondary to neurofibromatosis. Third nerve palsy may lead to hypotropia even when there has been some recovery. In all these disorders it is necessary to defer surgery to improve the ptosis until the best vertical alignment of the visual axes has been obtained. The results of surgery on 12 hypotropic eyes is the subject of this study.

Patients and methods

All patients attended Moorfields Eye Hospital, London, between October 1979 and November 1982. The majority (9/12) had been referred to one of us (JROC) for consideration of surgery for ptosis. The age range was from 5 to 23 years, mean 12.5 years. There were six females and six males (Table 1). Seven patients had congenital ptosis with hypotropia of the ipsilateral globe. Two patients had buphthalmos with ptosis due to neurofibromatosis. Two patients had third nerve palsy with misdirection, one congenital, the other due to a motor cycle accident. One patient had Marcus Gunn jaw-winking syndrome.

VISUAL ACUITY

Eight patients had deficient visual acuity in the affected eye. In five cases this was thought to be due to amblyopia, in two cases complicated by high myopia. The two eyes affected by neurofibromatosis had the very poor acuities of 6/60 and light percep-

tion. The patient with the traumatic third nerve palsy also suffered extensive damage to the anterior visual pathways with extensive field loss, worse in the paretic eye, and evidence of chiasmal damage.

PREOPERATIVE DEVIATION

All cases showed hypotropia in the primary position, increasing on upgaze. The size of the deviation ranged from 9 prism dioptres to 70 prism dioptres, with a mean of 30.5 prism dioptres. All cases showed deficient elevation of the affected eye. Eight cases had an associated horizontal deviation of greater than 10 prism dioptres. Four had an esodeviation, four had an exodeviation. The two cases of third nerve palsy showed signs of misdirection with elevation of the lid on adduction and especially on depression in adduction. Seven cases showed pseudoptosis with elevation of the lid to near-normal height when the hypotropic eye was forced to take up fixation.

BINOCULAR VISION

Two cases could fuse targets in the lower field of gaze, with a symmetrical cross on Bagolini striated glass testing and stereoacuities of 60 and 140 seconds of arc respectively on the Titmus stereotest. Both suppressed the hypotropic eye on upgaze.

PREVIOUS SURGERY

Four cases (nos. 1, 3, 5, and 8) had undergone previous extraocular muscle surgery. Of these one had had superior rectus resection only, two had had combined superior rectus resection and inferior rectus recession, and one (case 8) with congenital third-nerve palsy had a history of three previous procedures on the horizontal recti of both eyes.

Six cases (nos. 1, 3, 4, 5, 9, and 10) had undergone

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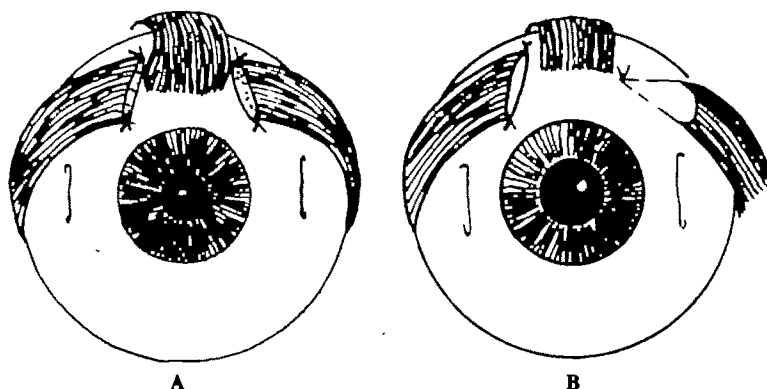


Fig. 1 A: Knapp procedure. Horizontal rectus muscles are elevated and sutured to the globe in order to straddle the superior rectus insertion. B: Modified Knapp procedure. The technique is similar to that in the standard Knapp procedure, but the suture for the recessed muscle is brought through long scleral bites and tied adjacent to the superior rectus insertion.

previous surgery for ptosis, usually some form of levator resection. Two cases had also had frontalis suspension procedures. In three cases the amount of levator resection was known, the figures being 10, 12, and 13 mm.

SURGERY

In 10 of the cases the operation was performed by one of us (JPL). Eleven cases were treated with Knapp¹ procedures or a modification of it. The horizontal recti were transposed to the superior rectus insertion so as to straddle it (Fig. 1A). In eight cases a significant horizontal deviation was present. Six cases had a modification of the standard procedure with appropriate amounts of horizontal rectus recession and resection. Where a muscle was recessed, the points of reattachment were measured from the superior rectus insertion. Initially, two separate scleral sutures were inserted. More recently, a 'hang back' technique (Fig. 1B) has been utilised.

Eleven cases had preoperative forced duction testing of the affected eye under general anaesthesia before the start of surgery. In eight cases (66%) this was judged to show resistance to passive elevation of the globe. Seven cases were treated with inferior rectus recession in addition to the basic elevation procedure (in one case at a subsequent date). The eighth case had the area of the inferior rectus explored. The muscle was found to be surrounded by a condensation of fibrous tissue. When the muscle was dissected free, the traction test improved markedly, and the muscle was therefore not recessed. A similar case was reported by McNeer and Jampolsky.⁷

One case underwent the procedure described by Callahan,⁴ where the horizontal recti and superior rectus are split without disinsertion and are joined in a similar manner to the Jensen⁸ procedure for lateral rectus palsy (Fig. 2). This patient, a 12-year-old boy with von Recklinghausen's neurofibromatosis, had a

buphthalmic right eye in conjunction with a right ptosis partly due to a plexiform lid neuroma. The visual acuity of the eye was perception of light. There was extensive scleral thinning with staphyloma formation, especially superiorly (Fig. 3). He had a right Callahan procedure in April 1981. This procedure was preferred because of the technical difficulty of resuturing rectus muscles to the very thin sclera.

Results

In all cases the hypotropia was reduced as a result of surgery. The data are given in Table 1. The reduction in vertical deviation ranged from 7 to 40 prism dioptres. In those cases where additional recession-resection had been performed the horizontal devia-

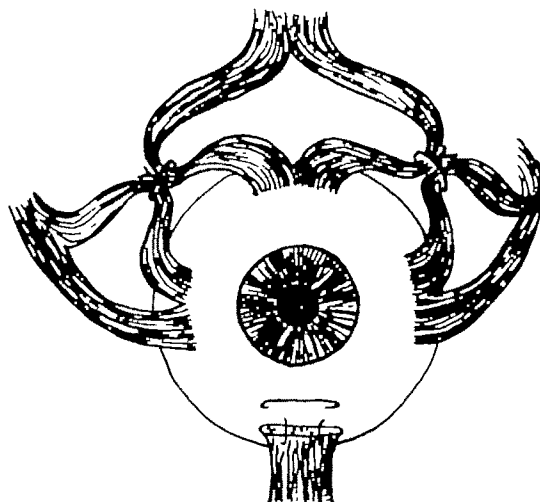


Fig. 2 Callahan procedure. The horizontal recti are split, as is the superior rectus, and the muscle strips joined with non-absorbable sutures. In addition the inferior rectus is recessed.

Table 1 Results

Case	Age Sex	Corrected VA %	Aetiology	Previous squint surgery	Previous ptosis surgery	Preop. deviation (prism dioptres)	Binocular vision preop.
1	13 F	6/9 6/9	Congenital ptosis with hypotropia	RSR+	Yes—nature unknown	R hypo 11 R eso 6	Fusion on downgaze
2	13 F	6/9 6/60	Neurofibromatosis	No	No	L hypo 60 L eso 40	No
3	12 F	6/6 6/6	Congenital ptosis with hypotropia	LIR— LSR+	L levator resection 1979	L hypo 25 L eso 4	Fusion on downgaze
4	13 F	6/36 6/9	Congenital ptosis with hypotropia	No	R levator resection 1972, R frontalis sling 1975	R hypo 29 R eso 10	No
5	9 M	6/24 6/5	Congenital ptosis with hypotropia	RIR— RSR+ 1979	R levator resection 1979	R hypo 9 R eso 16	No
6	20 M	6/60 6/5	R traumatic IIIIn palsy. Misdirection. R optic atrophy and chiasmal damage	No	No	R hypo 11 R eso 30	No
7	12 M	PL 6/5	Neurofibromatosis	No	No	Gross R hypo Mod. R eso	No
8	7 M	6/9 6/6	Congenital R IIIIn palsy + misdirection	1975 { 1977 { 1979 { RLR— RMR+ RMR— RIR+ LMR— LLR+	No	R hypo 11 R eso 40 Variable	No
9	14 F	6/5 6/18	Congenital ptosis with hypotropia, L myopia	No	L ptosis surgery 1969—L levator resection	L hypo 30 L eso 6	No
10	15 F	CF 6/5	Marcus Gunn jaw-winking syndrome, R myopia	No	1971—levator resection, 1979—R frontalis sling	R hypo 20 R eso 36	No
11	23 M	6/6 6/6	Congenital L ptosis with hypotropia R myopia	No	No	L hypo 65–70 L eso 24	No
12	5 M	6/6 6/24	Congenital ptosis with hypotropia	No	No	L hypo 40 Mod L eso	No

SR=superior rectus, IR=inferior rectus, MR=medial rectus, LR=lateral rectus, ARC=anomalous retinal correspondence.
Eso=convergent squint, Exo=divergent squint, Hypo=hypotropia, —=Recession, +=Resection.

Pseudoptosis	Surgery	Traction test	Complications	Postop binocular vision	Postop deviation (prism dioptres)	Correction (prism dioptres)
Yes	24 Oct 79 R Knapp procedure	Not done	R lower lid retraction	Improved field of BSV	R exo 16	11 R hypo
No	29 Nov 79 L Knapp procedure LLR+6 mm LMR-5.5 mm LIR-5 mm	Pos.	No	No	Improved	
Yes	L Knapp procedure 10 Mar 80	Neg	No	Improved field of BSV	No hypo exo 2	25 L hypo
Yes	12 May 80 R Knapp procedure + IR freeing	Pos	No	No	R hypo 3 R exo 6	26 R hypo
Yes	14 Jul 80 R Knapp procedure	Neg.	No	No	R hypo 2	7 R hypo
No	12 Feb 81 R Knapp + RLR-10 mm RMR+7 mm 2 Apr 81 RIR-4 mm	Pos.	No	No	Straight in primary position	11 R hypo 50 R exo
Minimal	2 Apr 81 R Callahan procedure + RIR-4 mm	Pos	No	No	Less R hypo More R exo	
Yes	16 Jun 81 R Knapp procedure RLR-4 mm RMR+5 mm RIR-3 mm	Pos	Mild Periorbital cellulitis	No	No vertical R exo 20	11 R hypo 20 R exo
Yes	17 Sep 81 L Knapp procedure	Neg	No	Vertical ARC (see text)	L hypo 4 + latent component	26 L hypo
No	17 Dec 81 R Knapp procedure RLR-3 mm RMR+3 mm RIR-3 mm	Pos.	No	No	R hypo 12 R exo less	8 R hypo
Minimal	15 Jul 82 L Knapp procedure LLR-5 mm LMR+3 mm LIR-5 mm	Pos	No	Present after R surgery (see text)	L hypo 30 L exo 4	40 L hypo 20 L exo
Yes	18 Nov 82 L Knapp procedure LMR-5 mm LIR-5 mm	Pos	No	No	No vertical Small L exo	40 L hypo



Fig. 3 Case 7 preoperatively.



Fig. 4 Case 7 after right Callahan's procedure.

tion was reduced. There was no significant difference between the size of the correction when the groups with and without inferior rectus recession were compared, the average corrections achieved being 23 and 19 respectively. In general the improvement was in reduction of the vertical deviation in the primary position, with persistently poor elevation and an increase in the deviation on upgaze. All patients or their parents reported cosmetic improvement. There were no overcorrections.

Case 7, the only case treated with a Callahan procedure, showed a reduction of hypotropia (Fig. 4) but an increase of esotropia to greater than 45 prism dioptres.

COMPLICATIONS

These were minor. Case 1 developed lower lid retraction, later treated with a scleral graft to the lower tarsus. Case 8 developed mild periorbital cellulitis which swiftly resolved on antibiotic therapy. There were no cases of postoperative uveitis or anterior segment ischaemia.

POSTOPERATIVE BINOCULAR VISION

The two patients with demonstrable fusion in down-gaze preoperatively had an extension upwards of their binocular area while still suppressing on upgaze.

Two other patients showed binocular vision post-operatively that had not been detectable pre-operatively.

Case 9. This 14-year-old white schoolgirl had congenital left ptosis (Fig. 5). The acuity of the right eye was 6/5, with a refraction of -0.25 dioptre. The left eye's corrected acuity was 6/18, with a refraction of $+0.50$ DS/ -5.00 DC $\times 175^\circ$. There was a left ptosis with 6 mm of levator function. There were 30 dioptres of left hypotropia and 3° of left exotropia. Orthoptic testing preoperatively showed 'left suppression.' A Knapp procedure performed on 17 September 1981 improved the hypotropia (Fig. 6). She was then found to have a vertical form of anomalous correspondence, with anomalous fusion at left hypo 4 prism dioptres, with an angle on dissociation of 22–28 prism dioptres.

Case 11. This 23-year-old Asian male student had a congenital left ptosis. The refraction of the right eye was -5.00 DS, giving an acuity of 6/6. The left refraction was -0.50 DS, giving an acuity of 6/6. With spectacles he fixed with the right eye and had a left hypotropia of 65–75 prism dioptres, and a left exotropia of 12° . Without spectacles he fixed with the left eye, adopting a chin-up head posture, and showed a marked right hypertropia. There was a left ptosis of 5 mm with about 5 mm of levator function.



Fig. 5 Case 9 preoperatively.



Fig. 6 Case 9 after left Knapp procedure.

On preoperative testing no evidence of binocular function could be found. A left Knapp procedure with inferior rectus recession and horizontal rectus recession/resection was performed on 15 July 1982, with reduction of the deviation to 30 prism dioptres of left hypotropia. On 30 September 1982 he underwent a right superior rectus recession of 5 mm, with posterior fixation sutures at 14 mm from the insertion. Remarkably, after this he showed fusion, with a 15° range of motor fusion on the synoptophore, a symmetrical cross on the Bagolini striated glass test, and a stereoacuity of 80 seconds of arc on the Titmus stereotest.

Discussion

The technique of elevation of the horizontal rectus insertions to relieve hypotropia is usually termed the Knapp procedure, although Dunlap⁴ has pointed out that Alvaro,⁷ Watson,⁸ and Dunlap himself⁹ described the procedure before Knapp's own description² in 1969. He reported 15 patients in whom the procedure gave a correction from 21 to 55 prism dioptres of vertical deviation. Two cases also had inferior rectus recession. Six of his patients had had unsuccessful Berke-Motais procedures, with an attempt to elevate the ptotic lid with a slip from the superior rectus. He found little effect on horizontal rotations, and noted that elevation remained poor, even when a good result was obtained in the primary position. In 1981 Callahan⁴ reported three cases of failed ptosis surgery in the presence of hypotropia of the affected eye. He described a new procedure in which the superior and horizontal recti were split and united similarly to the Jensen procedure. Inferior rectus recession was also performed. The rationale was that the anterior ciliary circulation would be less affected by such surgery, as the recti were not disinserted. Our experience is confined to one patient, in whom the hypotropia was improved, but a pre-existing esotropia was worsened. We cannot therefore recommend the procedure, but it may be of value in older patients where anterior segment ischaemia is a risk with detachment of rectus muscles.

In general we find the Knapp procedure reliable, especially where there is a pre-existing horizontal deviation, as appropriate adjustments of horizontal rectus muscle forces may be incorporated. The literature on 'double elevator palsy' is somewhat confusing in that some authorities, such as Dunlap,⁴ apply the term only to cases without mechanical restriction of elevation. He reported 22 cases of double elevator underaction, 16 of whom had supra-placement of the horizontal recti, 10 having horizontal recession/resection in addition. Results were generally good, and he provided a table of average

correction in prism dioptres per millimetre of supra-placement.

Other authors have used the term to describe a group of patients with unilateral ptosis and hypotropia, and have emphasised the necessity of detecting inferior rectus restriction by a preoperative traction test. Scott and Jackson¹⁰ reported a high incidence (11/15) of inferior restriction and considered that this represented a form of secondary contracture. They described two signs which they thought were commonly associated with inferior restriction. These were deficient Bell's phenomenon and an accentuation of the lower lid fold on attempted upgaze of the affected eye. McNeer and Jampolsky³ reported a case in which an additional anomalous insertion of the inferior rectus was found at surgery. Division of this improved rotations and led to a good cosmetic result. Case 4 in our series is reminiscent of this.

Metz¹¹ studied a series of patients with limited vertical movement of one eye. Nine of 15 were hypotropic in the primary position. Of these cases five had normal saccadic velocities in an upward direction and a positive forced duction test. The remaining four had reduced upward saccadic velocity, only one having a positive forced test. He concluded that, where the hypotropia was of mechanical origin, horizontal rectus transposition was not indicated. He also observed that the cases without hypotropia in primary gaze but with defective elevation all had inferior restriction. Cases with hypotropia in the primary position had a 50% chance of having a positive forced duction test.

Recognising that our series is a more heterogeneous group than that reported by other authors we performed a Knapp procedure (or Callahan procedure) on all patients, with an inferior rectus recession if the forced duction test was positive. In one patient the inferior rectus surgery was performed three months later. The inferior bulbar conjunctiva was also recessed if it seemed to cause restriction. Two problems might have resulted from this surgical approach: anterior segment ischaemia, which we did not encounter, doubtless owing to the youth of our patients, and overcorrection of the hypotropia. None of our cases was overcorrected, though overcorrections have been reported in other authors' series. Our average correction of hypotropia was 21 prism dioptres.

Barsoum-Homsy¹² reported six cases of congenital double elevator palsy with results of Knapp procedures in four. Her average correction was 31.7 prism dioptres. She reviewed the literature, quoting Watson,⁸ who obtained an average correction of 30.5 prism dioptres, Knapp,² with an average correction of 38 prism dioptres (however, 40% of his cases were

post-Berke-Motais procedures), Cooper and Greenspan¹³ with an average of 26.6 prism dioptres, and Scott and Jackson,¹⁴ who obtained an average shift of 37 prism dioptres but overcorrected three of five patients.

All authors are in agreement that any ptosis surgery contemplated should be deferred until the best ocular alignment has been achieved. Six of our 12 patients had previous surgery that failed to elevate the lid, usually a levator resection. In addition three had had attempts to elevate the globe by surgery on the vertical recti. Not all of the previous records were available to us, but where they were they showed poor results from superior rectus resection. Presumably the superior rectus in these cases was either paretic or congenitally hypoplastic in association with levator muscle dystrophy. Furthermore, Beard¹⁴ states that superior rectus resection is liable to increase the apparent ptosis by an indirect effect on the levator.

Finally, there are the interesting and unexpected results in cases 9 and 11, which appeared to show a sudden acquisition of binocularity after the surgery was completed. In case 9 this appeared to be a vertical form of anomalous correspondence, whereas in case 11 there appeared to be bifoveal fixation and fusion. Each patient had a clear history of the ptosis and hypotropia being present from birth. Both were unilaterally myopic and had worn their correction constantly with relatively good vision in the myopic eye in case 9, while case 11 preferred to fixate with the myopic eye when wearing spectacles. It is well recognised that patients with double elevator palsy may have binocular function in downgaze with suppression elsewhere. Two other patients in this series showed this. Although neither case 9 nor 11 could be shown to be able to fuse in downgaze before surgery, it seems plausible to assume that they represented extreme forms of this adaptation. Certainly the other references to vertical anomalous correspondence that we have been able to locate¹⁵⁻¹⁷ do not appear to be comparable.

CONCLUSIONS

Hypotropia and ptosis, with or without pseudoptosis, has been treated surgically in 12 patients, 11 with Knapp procedures, one with a Callahan procedure. Improvement was obtained in all cases, the correction ranging from 7 to 40 prism dioptres with no over-corrections. It is concluded that these are safe and effective procedures in this situation and should be considered prior to considering direct surgical intervention for the ptosis.

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Presentation White, microfine, sterile ophthalmic suspension containing fluorometholone 0.1%. **Uses** Topical ophthalmic suspension for steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye. **Dosage and Administration** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 3 drops every hour. Care should be taken not to discontinue therapy prematurely. **Contra-indications, Warnings, etc.** **CONTRA-INDICATIONS:** Acute superficial herpes simplex keratitis. Fungal diseases of ocular structures, vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity to the constituents of this medication. **Warnings:** Steroid medication in the treatment of herpes simplex keratitis involving the cornea requires great caution. Frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the cornea, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or a perforation has been known to occur with use of topical steroids. Safety and effectiveness have not been demonstrated in children of the age group two years or below. This preparation contains benzalkonium chloride and should be used with caution in contact with hydrophilic contact lenses. **Use in Pregnancy** Safety of the use of topical steroids during pregnancy has not been established. **Precautions** As fungal infections of the cornea are particularly prone to develop coincidentally with long term steroid therapy, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intra-ocular pressure should be checked frequently. **Adverse Reactions** Glaucoma with optic nerve damage, visual acuity or field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of the cornea. Local side effects of steroid therapy ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Protect from freezing. **Legal Category** POM. **Package Quantities** Supplied in plastic dropper bottles of 5ml and 10ml. Basic NHS cost as at July 1988: 5ml £1.78, 10ml £2.83. PL 0426-0028. Full prescribing information is available on request.

FML-Neo^{*} PRESCRIBING INFORMATION

Presentation Sterile, white, microfine ophthalmic suspension containing fluorometholone, NF0 1% and neomycin sulphate, BP0 5% (equivalent to 0.35% neomycin base). **Uses** FML-Neo^{*} is indicated for the management of steroid responsive inflammation of the palpebral or bulbar conjunctiva, cornea and anterior segment of the globe, when threatened or complicated by infection with neomycin-sensitive organisms. **Dosage and Administration** One or two drops in the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosage may be safely increased to one drop every hour. Care should be taken not to discontinue treatment prematurely. Shake well before using. **Contra-indications, Warnings, etc.** Acute untreated purulent ocular infections. Acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the conjunctiva and cornea. Ocular tuberculosis, fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As for FML^{*} above and, in addition in diseases due to micro-organisms resistant to neomycin, infection may be masked enhanced or activate the steroid. Prolonged use may result in overgrowth of nonsusceptible organisms. Articles in current medical literature indicate increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind. If sensitive or other untoward reactions occur, discontinue the medication. **Precautions** Patients with histories of herpes simplex keratitis should be treated with caution. Use of topical steroids may increase intraocular pressure. Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated. Local side effects of steroid therapy ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Shake well before using. Do not freeze. **Legal Category** POM. **Package Quantities** Available in 5ml plastic dropper bottles. Basic NHS cost as at July 1988: £1.90. PL 0426-0043. Prescribing information is available on request.

*Trade Mark



Adrenaline



Pilocarpine

ABRIDGED PRODUCT INFORMATION

Full prescribing information is available and should be consulted before prescribing.

USES

Elevated intra-ocular pressure including: ocular hypertension, chronic open-angle glaucoma (including aphakia); secondary glaucoma.

DOSAGE AND ADMINISTRATION

Usually one drop 0.25% solution in affected eye twice a day. If necessary change to one drop 0.5% solution twice a day.

CONTRA-INDICATIONS

Bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock. Hypersensitivity.

PRECAUTIONS

'Timoptol' may cause side effects of systemic beta-blockade. Cardiac

failure should be adequately controlled before prescribing. History of severe cardiac disease requires monitoring for cardiac failure and checking of pulse rates. Respiratory and cardiac reactions (including death) have been reported.

Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade. Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most cases clear on withdrawal. If seen, beta-blockers should be withdrawn gradually.

Do not use in patients with soft contact lenses.

Mydriasis resulting from use of 'Timoptol' with adrenaline reported occasionally. Potentially, hypotension and/or marked bradycardia may result from addition of 'Timoptol' to a calcium antagonist, rauwolfia alkaloid or beta-blocker.

Children: Not recommended.

Data not available for use in children.

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Nursing: Mother should either stop nursing or stop 'Timoptol'.

Pregnancy: Not studied; weigh benefit against possible hazards.

SIDE EFFECTS

Ocular irritation, including conjunctivitis, blepharitis, keratitis, blepharoptosis, and decreased corneal sensitivity. Visual disturbances, including refractory changes (due sometimes to withdrawal of miotics), diplopia, and ptosis.

Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischaemia, congestive heart failure, palpitation, cardiac arrest.

Bronchospasm (predominantly with pre-existing bronchospastic disease), respiratory failure, dyspnoea.

Headache, asthenia, nausea, dizziness, depression. Hypersensitivity, rash and urticaria.

Reactions with an unestablished relationship are ACMO, dry mouth,

anorexia, dyspepsia, nausea, dizziness, CNS effects (e.g. fatigue, behavioural changes and other psychic disturbances), hypertension and retroperitoneal fibrosis.

BASIC NHS COST

0.25% Ophthalmic Solution 'Timoptol'; £5.18 per 5 ml pack.

0.5% Ophthalmic Solution 'Timoptol'; £5.82 per 5 ml pack.

PRODUCT LICENCE NUMBERS

0.25% Ophthalmic Solution 'Timoptol'; 0025/0134.

0.5% Ophthalmic Solution 'Timoptol'; 0025/0135.

PRODUCT AUTHORISATION NUMBERS

0.25% Ophthalmic Solution 'Timoptol'; 35/53/2.

0.5% Ophthalmic Solution 'Timoptol'; 35/53/3.

Agents in the Republic of Ireland: Cahill May Roberts, P.O. Box 1090, Chapelizod, Dublin 20.

Issued April 1985

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Simultaneous bilateral primary diffuse malignant uveal melanoma: case report with pathological examination

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SUMMARY A 50-year-old Japanese housewife became blind owing to bilateral diffuse malignant melanoma of the choroid, ciliary body, and iris. These were histologically proved when enucleation was required because of blind painful eyes with raised intraocular pressures. She presented with reduced visual acuity and night blindness. Small scattered atrophic areas were observed between disc and macula on both sides, which fluorescein angiography showed were due to patchy atrophy of the retinal pigment epithelium. There was reduced amplitude in the electroretinogram. Inferior retinal detachments soon appeared and spread to become total. Pathological examination showed diffusely thickened choroid on both sides, due to infiltration by epithelioid and spindle-shaped malignant melanoma cells, which also affected the thickened ciliary body and iris diffusely. A carcinoma of the uterus successfully treated three years previously and the probably multicentric origin of the malignancy in each eye, and its bilateral occurrence, suggest a tumour-producing tendency in this patient, an interpretation which also applies to one of the other eight reported cases.

This case of simultaneous, bilateral, histologically proved diffuse malignant choroidal melanoma in a 50-year-old Japanese housewife is being described because of the rarity of melanomata in the Japanese compared with Europeans and North Americans, the extreme rarity world wide of bilateral cases, and also because of the very unusual clinical presentation. Because she had a carcinoma of uterus three years previously a general predisposition to tumour formation is suggested in our patient (and others in the literature).¹⁻³

It has been estimated that 0.02 to 0.06% of all patients with eye disease have choroidal melanoma.⁴ The frequency of occurrence of ocular malignant melanoma in the general population of the USA is around 5 per million,⁵ while in Japan the only relevant report can be interpreted as suggesting an incidence of 0.5 per million, or 1/10th the USA incidence. Consistent with these figures are those of

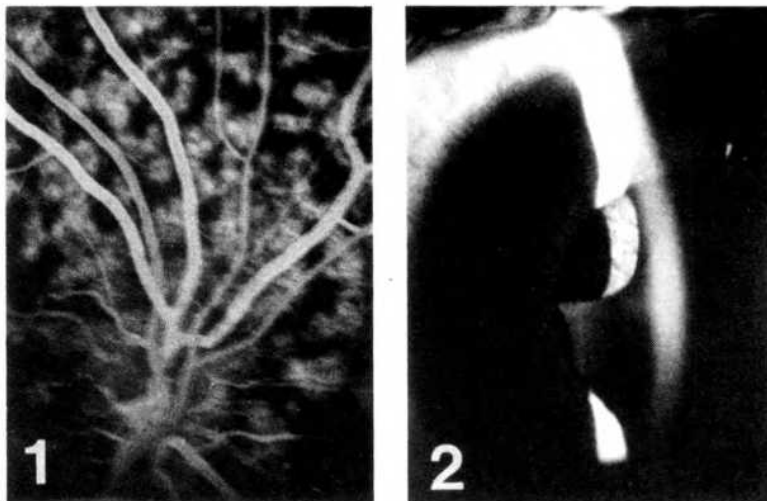
Hogan and Zimmerman⁶ giving a Caucasian:non-Caucasian ratio of 250:1 in cases of melanoma in the Washington Registry of Ophthalmic Pathology, and a ratio of 165:1 for Caucasians:Negroes.⁴

Bilateral cases of primary malignant melanoma are very unusual. Until 1949 Cordes and Cook's detailed review revealed only six reports, of which two may have been of tuberculous lesions rather than malignant melanomas.⁷ In three others the diagnosis was presumed on clinical evidence only, but in the sixth case⁸ there was histological proof. They added a case of simultaneous melanoma in the right iris and left choroid, both confirmed histologically. Reese⁹ mentions a bilateral case. Of particular interest to us is the patient with bilateral proved choroidal melanoma described by Wiesinger *et al.*¹ because of the coexistence of meningioma and leukaemia. Three further cases of bilateral choroidal malignant melanomas, verified histologically, have been reported more recently.¹⁰⁻¹² Shamma and Watzke² estimated an incidence of bilateral cases of one per 50 million lifetimes, implying an occurrence once in 18 years in the whole USA.

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Fig. 1 Fluorescein angiography: late phase (18 seconds). Multiple patchy windows show in pigment epithelium, with increased leakiness of choroidal (tumour) vasculature.

Fig. 2 Left eye. Cyst arising in posterior layers of iris protruding at pupil margin at 10 o'clock. ($\times 7$).



Case report

A 50-year-old Japanese housewife presented to the Branch Hospital of Tokyo University with blurred vision and difficulty in coping with light-dark transition for one month. She had no previous eye disease, and the only important abnormality in her general health was an hysterectomy three years previously for uterine carcinoma, followed by 40 days' treatment with intravenous Endoxan or Cytosan (cyclophosphamide) 400 mg daily. The family history was negative and her parents were not consanguineous.

Positive ophthalmic findings were as follows. Corrected visual acuities were 0.4 in the right eye and 0.5 in the left. Multiple, atrophic patches of various sizes were scattered between disc and macula on both sides (recognised in retrospect as being unusual clinical features of diffuse malignant melanoma). On the right side drusen-like but white patches were also present in the macular area. Fluorescein angiography showed patchy atrophy of the retinal pigment epithelium (Fig. 1).

Dark adaptation curves had a reduced scotopic component, and the electroretinogram (ERG) showed reduced amplitude to stimuli of all intensities.

Negative findings at presentation were normal fields, pupil reactions, and ocular movements, and normal ocular tensions: Schiøtz right eye 6.5/5.5 g, left eye 6.0/5.5 g.

At that time the differential diagnosis included tapetoretinal dystrophy, metastatic carcinoma, and cyclophosphamide toxicity.

During the next two months, although the visual acuity (VA) improved to 0.7 in each eye, large

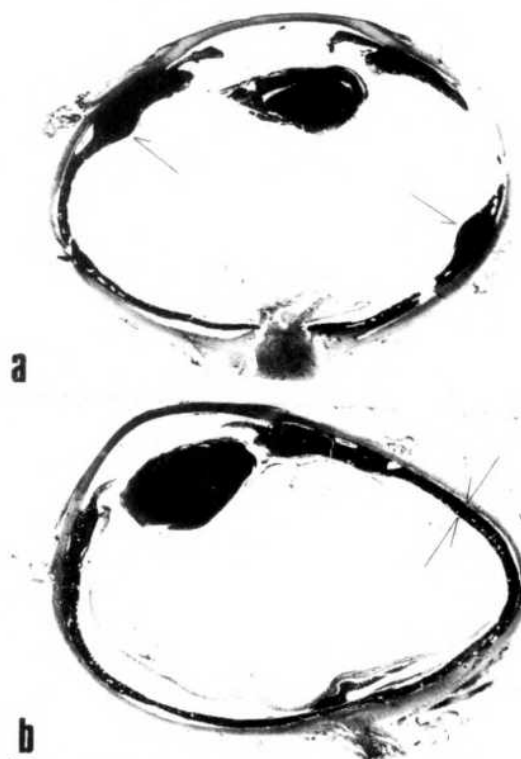


Fig. 3a Cross-section of the right eye showing diffuse thickening of the whole uveal tract and two nodules of melanoma, one on the nasal side near the ciliary body and the other three disc diameters temporal to the optic disc. Arrows indicate two nodules of melanoma. (Haematoxylin and eosin, $\times 2.6$). Fig. 3b Cross-section of the left eye showing diffuse thickening of the whole uvea. Arrows show thickness of the uvea. (Haematoxylin and eosin, $\times 2$).

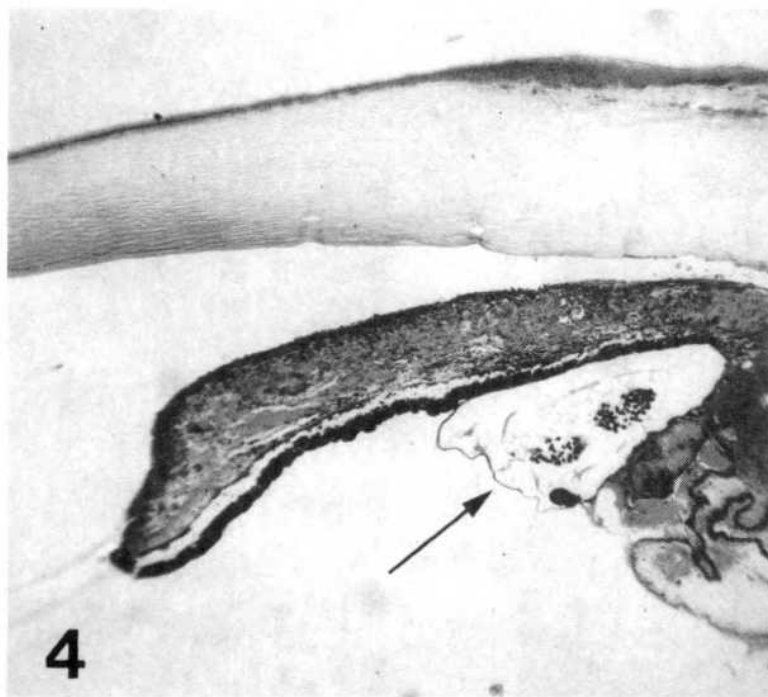


Fig. 4 Cross-section of the anterior part in right eye. Arrow indicates the formation of iris cyst including pigment-granule-containing cells. (Haematoxylin and eosin, $\times 30$).

bilateral inferior retinal detachments without holes appeared, with constricted fields, a more diminished ERG, and corresponding with the patient's increasing difficulty in seeing in dull illumination, a remarkably decreased dark-adaptation curve. A month later the VAs had diminished to hand movements RE and

0.01 LE because of an increase upwards in the extent of the retinal detachments, which probably also accounted for indistinctness ophthalmoscopically of the scattered white atrophic patches at the posterior pole, and reduced intraocular pressure (Schiotz: RE 12.0/5.5 g, LE 10.0/5.5 g).

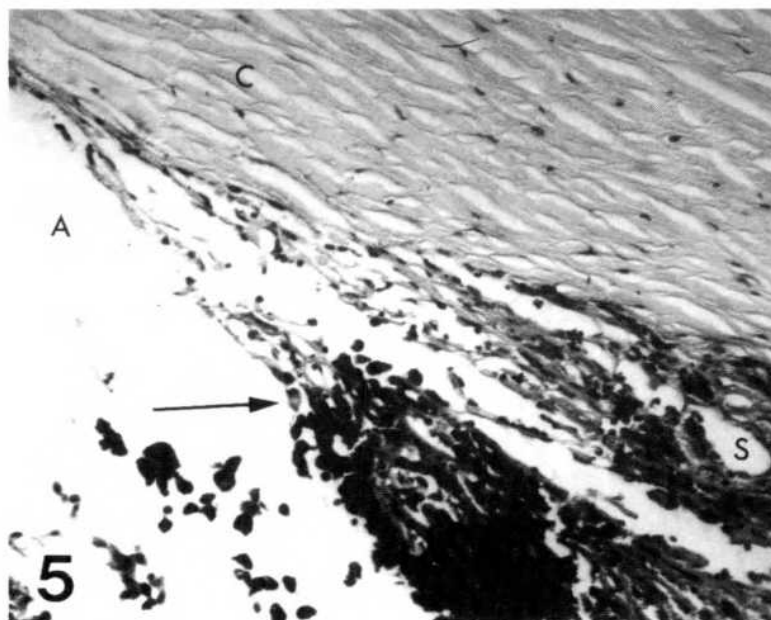


Fig. 5 Cross-section of the chamber angle in left eye. Arrow indicates melanoma cells infiltrating the trabecular meshwork. A=anterior chamber. C=cornea. S=Schlemm's canal. (Haematoxylin and eosin, $\times 187$).

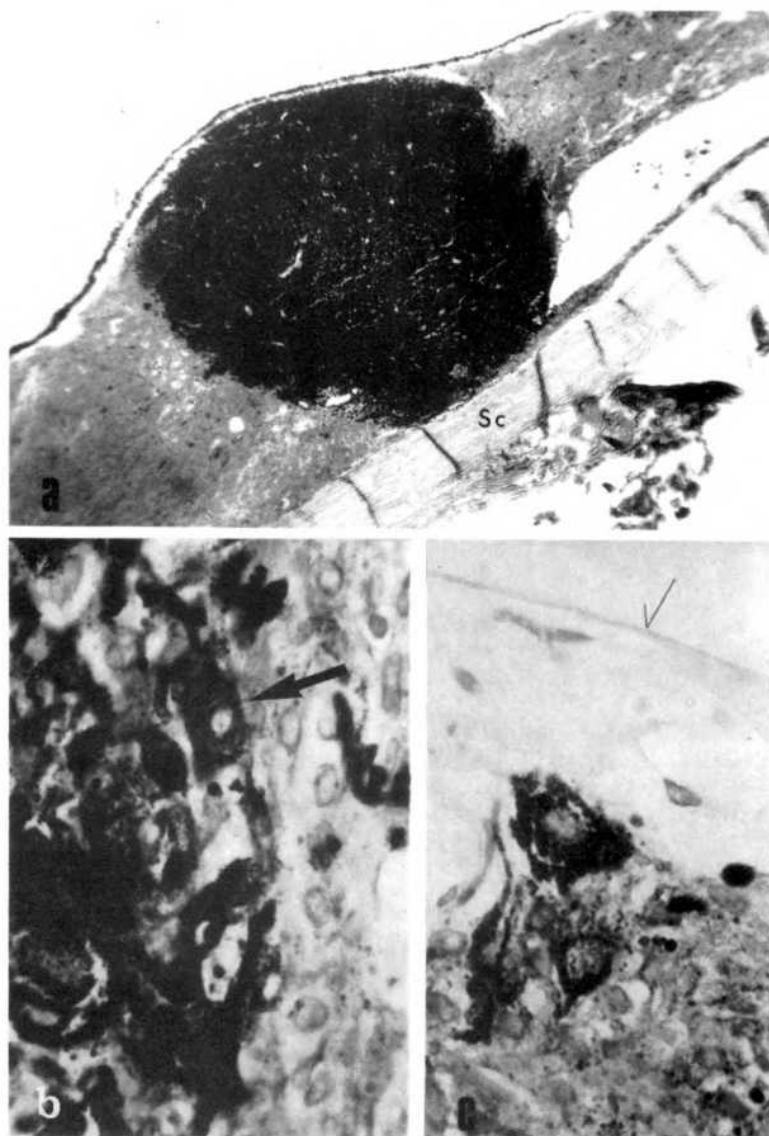


Fig. 6 Cross-section of the choroid in right eye. a. Abundant pigment containing cells form nodule. Sc=Sclera. b. High magnification of tumour cells. c. The same. (Haematoxylin and eosin, $\times 700$).

After six months from presentation both eyes were completely blind with total bilateral retinal detachments and dilated non-reacting pupils. Transillumination tests were negative. The only abnormality revealed by general medical investigation was an erythrocyte sedimentation rate (ESR) of 98 mm in 1 hour, 120 in 2 hours. A specimen of subretinal fluid showed a positive Rivalta reaction (supporting an exudative rather than a rhegmatogenous origin) but no cells or bacteria. Seven months after presentation an iris cyst appeared at the pupil margin at 10 o'clock in the left eye (Fig. 2).

Gamma scintillation examination of the skull, for

48 hours after ^{67}Ga by intravenous injection, showed an abnormal count in the region of both eyes.

About 11 months after her first attendance the left eye had to be enucleated because pain was added to blindness, with ocular tensions of Schiötz 4.0/10 g due to shallow anterior chambers and widespread goniosynechiae. Enucleation of the right eye had to be undertaken two months later for the same reason.

PATHOLOGICAL FINDINGS

Gross examination

The positive findings were total retinal detachments in both eyes, with diffusely thickened choroid and

ciliary body (Fig. 3a, b). In the right eye a pigmented nodule 3.4–4.0 mm in diameter and 1.7–2.0 mm in thickness was found three disc diameters temporal to the disc; another, with similar dimensions, was present on the nasal side adjacent to the ciliary body (Fig. 3a).

Microscopic examination

The positive findings were as follows:

(i) *Iris*. Epithelial malignant melanoma cells with abundant dark brown pigment granules had diffusely thickened the iris (Fig. 3). There was a cyst in the right eye at the root of the iris and its wall was partly adherent to the ciliary body. Its contents were an amorphous mass with small numbers of pigment-containing cells. In the left eye a membranous structure protruded towards the posterior chamber, presumptively part of an iris cyst (Fig. 4).

(ii) *Angle of anterior chamber*. Polygonal pigment-containing cells had infiltrated the trabecular meshwork and the area between it and the base of iris (Fig. 5).

(iii) *Ciliary body and choroid* were both thickened greatly by an infiltration of spindle and epithelioid cells, occasionally in mitosis, containing pigment granules which may have obscured nucleoli. Pigment granules measuring 0.5–0.7 μm , were of varying density and gave a negative Prussian blue reaction. The increased choroidal thickness was more marked in the left eye (0.7 mm when dehydrated) compared with the right (0.4 mm). The normal thickness is 0.1 mm. The nodules visible macroscopically in the right eye (Fig. 3) were confirmed to be of malignant melanoma tissue (Fig. 6a, b, c).

(iv) *Retinae* were totally detached and degenerate.

Acellular, serous, subretinal exudate was present. The pigment epithelium was partially preserved.

(v) *Sclera and optic nerve*. Spindle cells with elongated nuclei had infiltrated the region of the perforating scleral vessels, including the short ciliary arteries near the optic nerve head, which however was itself uninvolved in tumour spread (Fig. 7). No local spread of tumour beyond the sclera could be detected microscopically or macroscopically.

The cellular morphology corresponded with the 'mixed-cell type' of Callender's classification.¹³

Discussion

The clinical diagnosis was very difficult indeed because the melanomas were diffuse, causing very unusual symptoms and signs, and were bilateral, the latter condition being extremely rare. However, tumour was suspected. The previously treated carcinoma of uterus could well have recurred and caused bilateral metastatic deposits in the choroid, albeit with very unusual manifestations. Similarly, a toxic effect on the retina of the anticancer drug cyclophosphamide was considered as a possible cause. However, we suspect a tumour-producing tendency exists in this patient, first because *both* eyes are affected, secondly because within each eye we think a multiplicity of neoplastic centres arose, and thirdly the patient had a carcinoma of the uterus three years previously. Accordingly we suggest that it is no coincidence that another well-documented case of bilateral ocular malignant melanoma had a meningioma at the base of skull and a stem-cell leukaemia, which caused her death.¹ Recently a case of bilateral uveal melanoma in a 60-year-old woman

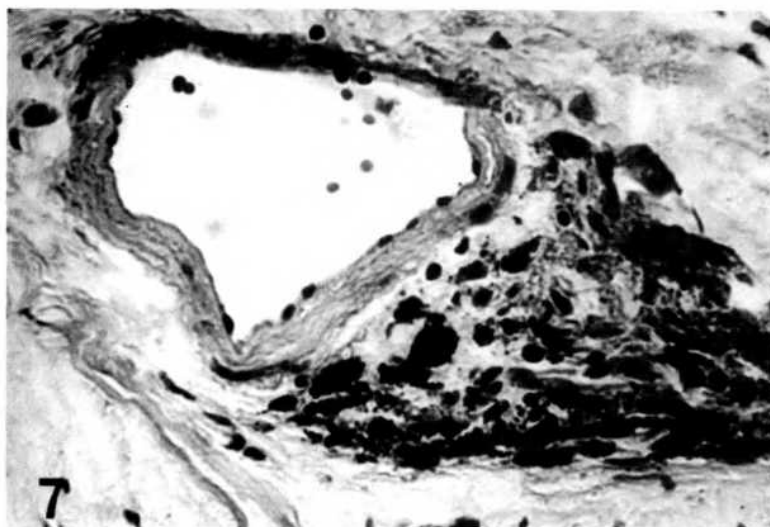


Fig. 7 Cross-section of short posterior ciliary artery, indicating the infiltration of tumour cells in the surrounding tissue. (Haematoxylin and eosin, $\times 700$).

in association with primary bilateral ovarian carcinoma was described.³ These cases seem to suggest the general predisposition to tumour formation. Analogously, the association between the retinoblastoma gene and subsequent development of tumours elsewhere, even in non-irradiated tissues, would support this suggestion.¹⁴

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A blind randomised cross-over trial comparing metipranolol 0.3% with timolol 0.25% in open-angle glaucoma: a pilot study

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SUMMARY A blind randomised cross-over study was conducted on 10 patients (20 eyes) to compare the effect in patients with open-angle glaucoma of metipranolol 0.3% with that of timolol 0.25% on intraocular pressure following one month's topical instillation with each preparation alone. There was no statistically significant difference in intraocular pressure reduction between these two preparations, and the ocular tolerance of both was good. There was no significant difference in the blood pressure, pulse, or pupil diameters of patients receiving either preparation.

Both timolol and metipranolol are non-selective beta-adrenergic blocking agents effective in lowering the intraocular pressure in both normal and glaucomatous eyes.^{1,2} They show minimal intrinsic sympathomimetic activity and membrane stabilising effect.^{3,4} In contrast to timolol, which has been intensively investigated, metipranolol is a relative newcomer to the field of ophthalmology and as yet is not freely available commercially. The present study was undertaken to compare the effect on intraocular pressure and systemic parameters (such as blood pressure and pulse) of these two compounds in the short term.

Patients and methods

Patients with characteristic discs and field changes of primary open-angle glaucoma, either controlled on single antiglaucoma therapy or presenting as new patients, were considered for inclusion. Patients with, or with a history of, cardiovascular disease or constrictive airways disease (whether receiving systemic therapy or not) were excluded from consideration. Patients with existing corneal disease or corneal scarring or a previous history of ocular surgery were also excluded from the study.

Ten patients (20 eyes) were included in the trial (six female, four male, mean age 71.8 years, range 53-84 years). Following a five-day wash-out period for those individuals already using antiglaucoma

topical therapy (a five-day wash-out period was considered to be sufficient, as those patients who were already receiving topical antiglaucoma therapy were receiving either adrenaline or pilocarpine) each patient had a two-day intraocular pressure curve measured (at times 0, 3, 7, 11, 24, 27, 31, and 35 hours, where time 0 was 0900 h on day 1 of the curve) by Goldmann applanation with the Haag-Streit slit-lamp while an inpatient in hospital and receiving no antiglaucoma medication. Pulse and blood pressure (after three minutes sitting) and pupil diameters were measured at 0900 h on the second day of each phasing.

Each patient was then randomly allocated with timolol 0.25% or metipranolol 0.3% to be instilled topically twice daily into each eye. Each patient was readmitted to hospital after four weeks therapy, and a further two-day phasing curve with blood pressure, pulse, and pupil diameter was measured as before.

The second preparation was then allocated to each patient (without a second wash-out period) and again instilled topically twice daily for a further four weeks, after which time the patients were readmitted for a final two-day phasing curve and repeat measurements of blood pressure, pulse, and pupil diameter.

The code, which was held in the Pharmacy Department, was not broken until the trial was completed. Any subjective side effects were noted. Metipranolol was provided as the drop Beta-Ophtiole (metipranolol hydrochloride pH 5.5 with benzalkonium chloride and PVP tear film stabiliser

Table 1 Pretreatment and post-treatment mean intraocular pressures for two patients showing poor or no response to therapy. Intraocular pressure is the mean of data during two-day phasing period ($\pm$ SD)

Patient number	Eye	Intraocular pressure (mmHg)		
		Pretreatment	Timolol 0.25%	Metipranolol 0.3%
5	Right	24.3 $\pm$ 1.98	28.5 $\pm$ 2.67	24.8 $\pm$ 2.75
	Left	26.0 $\pm$ 1.41	27.5 $\pm$ 4.38	25.9 $\pm$ 2.90
7	Right	22.9 $\pm$ 4.02	21.3 $\pm$ 2.87	21.1 $\pm$ 2.70
	Left	28.3 $\pm$ 3.84	25.0 $\pm$ 3.89	23.5 $\pm$ 3.51

Table 2 Intraocular pressure at pretreatment and after four weeks' therapy with timolol 0.25% or metipranolol 0.3%. Mean $\pm$ SEM ($n=20$)

Time (h)	Intraocular pressure (mmHg)		
	Pretreatment	Timolol 0.25%	Metipranolol 0.3%
0	25.7 $\pm$ 0.7	22.6 $\pm$ 1.0	21.7 $\pm$ 1.0
3	24.7 $\pm$ 0.8	22.4 $\pm$ 0.9	21.6 $\pm$ 0.6
7	25.1 $\pm$ 1.0	22.2 $\pm$ 0.8	20.4 $\pm$ 0.4
11	23.8 $\pm$ 1.1	21.4 $\pm$ 1.1	20.8 $\pm$ 0.7
24	25.9 $\pm$ 0.9	20.7 $\pm$ 0.7	20.9 $\pm$ 0.5
27	23.6 $\pm$ 0.6	20.8 $\pm$ 0.5	20.3 $\pm$ 0.4
31	22.4 $\pm$ 0.8	21.0 $\pm$ 0.8	20.1 $\pm$ 0.6
35	23.5 $\pm$ 1.1	20.7 $\pm$ 0.8	19.5 $\pm$ 0.9

with 170 μ g of metipranolol in one drop of 0.3% solution).

Results

All patients completed the study. Two patients complained of a slight and short-lasting burning sensation following topical instillation of metipranolol. There was a poor or no lowering of

Table 3 Mean intraocular pressure ($\pm$ SEM) using the average of the recordings made during the two-day phasing period for each patient

Eye (n)	Intraocular pressure (mmHg)		
	Pretreatment	Timolol 0.25%	Metipranolol 0.3%
Right eye (10)	23.9 $\pm$ 1.0	21.3 $\pm$ 1.0	20.5 $\pm$ 0.7
Left eye (10)	24.8 $\pm$ 0.9	21.6 $\pm$ 0.9	20.9 $\pm$ 0.7
Both eyes (20)	23.34 $\pm$ 0.69	21.47 $\pm$ 0.66	20.65 $\pm$ 0.48

intraocular pressure with metipranolol and timolol in two patients (Table 1). However, good control of intraocular pressure was achieved with both preparations in the remaining eight patients (16 eyes).

Table 2 shows the intraocular pressures (both eyes taken together) at pretreatment and after four weeks' therapy with either timolol 0.25% or metipranolol 0.3% during the two-day phasing period. These results are expressed graphically in Fig. 1. Table 3 shows the mean intraocular pressure (by eye) after four weeks' treatment with timolol 0.25% or metipranolol 0.3%.

Table 4 shows the mean reduction in intraocular pressure (both eyes taken together) during the two-day phasing period after treatment with timolol 0.25% and metipranolol 0.3%. The overall reduction in intraocular pressure for right and left eyes after four weeks' treatment with either of the two topical preparations (the mean of the two-day phasing results being taken) is shown in Table 5. The paired *t* test showed no statistically significant difference between the intraocular pressure reduction between metipranolol 0.3% and timolol 0.25%.

The mean blood pressure, pulse, and pupil diameters at pretreatment and following each therapy period are shown in Table 6. There was no statistically significant difference (paired *t* test) in

Fig. 1 Intraocular pressure at pretreatment and after four weeks' therapy with either timolol 0.25% or metipranolol 0.3% during the two-day phasing period.

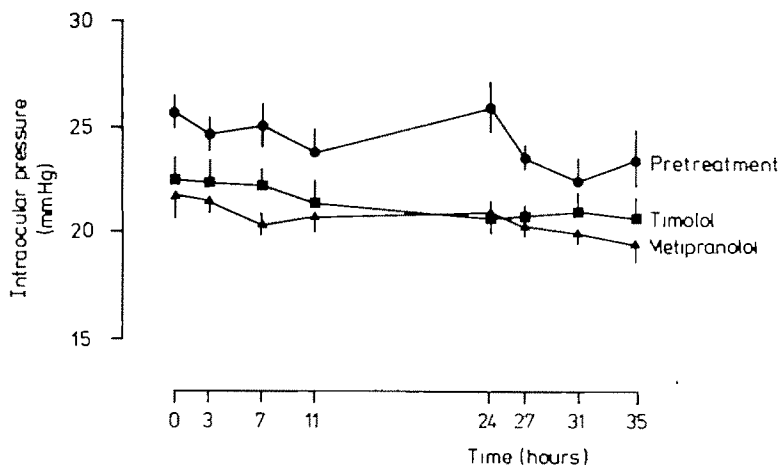


Table 4 Reduction in intraocular pressure during two-day phasing after treatment with timolol 0.25% or metipranolol 0.3%. Mean $\pm$ SEM ($n=20$)

Time (h)	Change in intraocular pressure from pretreatment values (mmHg)	
	Timolol 0.25%	Metipranolol 0.3%
0	-3.1 $\pm$ 1.0	-4.0 $\pm$ 1.0
3	-2.3 $\pm$ 0.7	-3.1 $\pm$ 0.5
7	-2.9 $\pm$ 0.9	-4.7 $\pm$ 0.7
11	-2.4 $\pm$ 0.8	-3.0 $\pm$ 0.8
24	-5.4 $\pm$ 0.9	-5.0 $\pm$ 1.1
27	-2.8 $\pm$ 0.7	-3.3 $\pm$ 0.6
31	-1.4 $\pm$ 0.8	-2.3 $\pm$ 0.8
35	-2.8 $\pm$ 1.3	-4.0 $\pm$ 1.2

Table 5 The mean reduction in intraocular pressure by eye mmHg (with SEM) (the mean of the two-day phasing period being taken for each patient) and significance (by the paired *t* test)

	Timolol 0.25%	Metipranolol 0.3%	Significance
Right eye	2.7 (1.2)	3.4 (1.0)	NS
Left eye	3.1 (1.0)	4.0 (0.8)	NS

Table 6 The mean (with SD) blood pressure, pulse, and pupil diameter (both eyes being taken together) at pretreatment and following timolol 0.25% and metipranolol 0.3% therapy

	Pretreatment	Timolol 0.25	Metipranolol 0.3%
Systolic blood pressure, mmHg	147 (17.67)	142 (12.95)	151 (20.28)
Diastolic blood pressure, mmHg	84.5 (8.96)	78.5 (6.69)	81.1 (6.97)
Pulse, beats/S	86.4 (13.7)	76.4 (4.53)	82.3 (11.01)
Pupil diameter, mm	2.55 (0.44)	2.6 (0.52)	2.6 (0.48)

blood pressure, pulse, or pupil diameter between either metipranolol 0.3% or timolol 0.25% and pretreatment values.

Discussion

This short-term trial indicates that there is no significant difference in the intraocular pressure-lowering effect between timolol 0.25% and metipranolol 0.3%. Although there was an 11% reduction in intraocular pressure after four weeks' therapy with timolol 0.25% as compared with a 15% reduction in intraocular pressure after metipranolol 0.3%, this difference was not statistically significant. Many studies have shown a reduction in intraocular pressure with timolol and metipranolol eye drops to

be greater than that recorded in this study^{5-9,10} (an average reduction of about 25%). If one analyses the results from those eight patients showing a response to both metipranolol 0.3% and timolol 0.25%, the intraocular pressure reduction from pretreatment values approximates to that shown by the cited authors.^{5-9,10}

Although a reduction of pulse rate and blood pressure was recorded following therapy for four weeks with both these treatment regimens, it was not significantly different. However, the results from 10 patients may be insufficient to identify any systemic problems in the short term, and as this was a pilot study it was of insufficient duration to identify any systemic problems occurring in the long term. The mild burning sensation noticed after metipranolol 0.3% instillation in two patients (20%) has been recorded elsewhere and is likely to be due to the lower pH of metipranolol (5.5) than of timolol. Denffer¹⁰ recorded a burning sensation following topical instillation of metipranolol in 45% of patients, but this sensation was insufficient in intensity to warrant discontinuance of the drug in any patient.

This trial would suggest that metipranolol 0.3% is a well tolerated non-selective beta blocking agent which appears to be as effective as timolol 0.25% in the reduction of intraocular pressure following short-term administration. Further trials are in progress to assess its long-term effectiveness and patients' tolerance of it.

We express our gratitude to Mrs Margaret Hercules, of the Pharmacy Department at Manchester Royal Infirmary for her help in the randomisation and allocation of treatment schedules. We thank Dr Mann Pharma, of Berlin, for supplying metipranolol eye drops. We express our gratitude to Kath Shawley, of Smith and Nephew Research, for her help in statistical analysis.

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Measurement of retinal blood flow in diabetes by the blue-light entoptic phenomenon

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SUMMARY Retinal blood flow velocity was measured in 24 normal volunteers and compared with the results obtained in 101 diabetics at different stages of retinopathy. The blue-light entoptic phenomenon was used to measure retinal flow velocity. Results showed that there was a significantly higher capillary flow velocity in those patients with background retinopathy (0.74 ± 0.32 mm/s) over the group of normals (0.54 ± 0.19 mm/s) and those diabetics with no retinopathy (0.51 ± 0.24 mm/s). Retinal flow velocity was reduced at the preproliferative stage of retinopathy to 0.37 ± 0.2 mm/s. Proliferative retinopathy showed a slightly greater flow velocity (0.56 ± 0.27 mm/s), which was reduced following photocoagulation (0.42 ± 0.14 mm/s).

Leucocytes flowing in macular capillaries can be observed by the blue-light entoptic phenomenon. When the subject looks into blue filtered light of wavelength 430 nm, the leucocytes appear as luminous dots with dark tails moving along curved paths. The motion of the leucocytes is 'pulsatile,' that is, the velocity increases and decreases in time with the systolic and diastolic phases of the cardiac cycle. This phenomenon can be used to measure retinal flow velocity. The technique, which involves matching the speed of 'simulated leucocytes' moving on a high-definition TV monitor to the speed of the subject's own leucocytes, was first described by Riva and Petrig¹ and is used in the Department of Diabetic Retinopathy at the Hammersmith Hospital in a slightly modified form. It has the advantage of being non-invasive, allowing examination of large numbers of patients and repeated examinations on the same patient. Its main disadvantage is that the measurement is subjective.

Material and methods

For the subject to estimate his own leucocyte flow velocity a BBC microcomputer (32 K) is programmed to produce on a high-definition TV monitor a pattern of dots ('simulated leucocytes') moving along curved paths against a blue background. The subject then alters the speed at which these dots are moving

until they match the speed of the subject's own leucocytes as seen in the entoptoscope. Simulation of the pulsatile motion is produced by a finger pulse monitor. The 'pulsatility'—that is, the difference between the minimum and maximum velocity attained during the motion of the dots—can then be altered by means of a separate control. Three results are produced, the maximum velocity (V_{max}) attained by the simulated leucocytes, the minimum velocity (V_{min}), and the mean velocity (V_{mean}), the value of which is calculated by integration of the changing velocity against time. A magnification factor which takes into account the distance between the monitor and the eye and a standard focal length for the eye then allows the mean velocity of dots on the monitor (V_{mean}) to be converted to mean leucocyte velocity at the retina.

All subjects in the study had to undergo a screening procedure to assess their ability to match the speed of the simulated leucocytes to the speed of their own leucocytes as seen in the blue-light entoptoscope. The screening involves two TV monitors both displaying a pattern of simulated leucocytes generated by a pair of BBC microcomputers (32 K). The subject controls the speed of the simulated leucocytes on the first monitor and has to match it to a speed, previously determined by the investigator, or a second monitor. This is done four times. Only those subjects who could match speeds with an accuracy of greater than 80% were included in the subsequent investigation.

Reproducibility studies were carried out to

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Table 1 Patient details

Retinal category	Number	Mean age years (range)	Duration diabetes mellitus years (range)
Non-diabetics	23	27.0 (20–39)	NA
No retinopathy	12	32.8 (21–51)	11.4 (2/52–28)
Background	38	41.4 (19–74)	19.9 (3–38)
Preproliferative	11	44.1 (23–64)	8.0 (2–14)
Proliferative	8	40.3 (24–59)	18.8 (6–31)
Photocoagulated	32	44.4 (20–63)	24.9 (3–42)

validate the technique. Fourteen non-diabetic volunteers from the Department of Medicine at the Hammersmith Hospital and 13 stable diabetic patients from the Diabetic Retinopathy Clinic had retinal flow velocity measurements made on the same eye on two occasions. Pulse and blood pressure were noted each time.

Patients attending the Diabetic Retinopathy Unit at the Hammersmith Hospital were recruited for a study investigating retinal blood flow velocity at different stages of retinopathy. They were divided into the following groups (patients with maculopathy were excluded) (Table 1): (1) no retinopathy (observable ophthalmoscopically or on colour retinal photographs); (2) background retinopathy (patients examined ranged in severity from a few microaneurysms only to multiple microaneurysms and haemorrhages); (3) preproliferative retinopathy (microaneurysms, cluster or large blot haemorrhages, cotton-wool spots, intraretinal microvascular

abnormalities, venous abnormalities of severe degree, but no new vessels); (4) proliferative retinopathy (disc and/or new vessels elsewhere); (5) post-photocoagulation (no evidence of new vessels remaining following argon or xenon treatment).

The results used are the mean of three readings taken at the same visit. Pulse, blood pressure, blood sugar (Beckmann glucose analyser), and HbA1 levels (Corning densitometer) were recorded each time. Student's *t* test was used to assess the significance of the results, *p* values of <0.05 were considered significant.

Results

The reproducibility in the 14 non-diabetics was 78.8%, the mean flow velocity being 0.74 mm/s (first occasion) and 0.79 mm/s (second occasion); only two subjects varied by more than 50%. Results were similar in the group of 13 diabetics. Reproducibility was 79%, mean flow velocities being 0.63 mm/s (first occasion) and 0.68 mm/s (second occasion) (Fig. 1).

Mean retinal blood flow velocity in a group of 24 normal volunteers (Table 2) was 0.54 mm/s (± 0.19).

In the diabetic group patients with no retinopathy (observable ophthalmoscopically) had a retinal blood flow velocity of 0.51 mm/s (± 0.24), which was not significantly different from that of the normal non-diabetic group. Examination of patients with background retinopathy showed a blood flow velocity of 0.74 mm/s (± 0.32), a significant increase over non-retinopathic subjects ($p < 0.02$) and normal

Fig. 1 Reproducibility of retinal blood flow measurements. Two flow velocity measurements (1st and 2nd) taken a few days or a few weeks apart. Reproducibility close to 80% in a group of 13 non-diabetic and 15 stable diabetic patients. Reproducibility: over 50% —; up to 50%

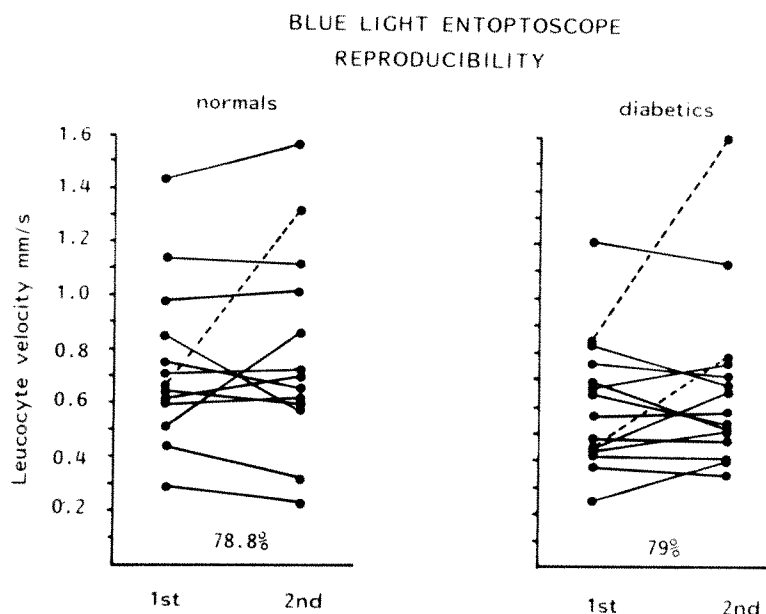


Table 2 Mean retinal blood flow in normal and diabetic groups

Retinal category	Total	Mean flow velocity (mm/s $\pm$ SD)	Mean HbA1 (% $\pm$ SD)	Mean blood pressure (mmHg $\pm$ SD)
Non-diabetics	23	0.54 $\pm$ 0.19	NA	112 $\pm$ 14.1/75 $\pm$ 5.6
No retinopathy	12	0.51 $\pm$ 0.24	8.0 $\pm$ 1.5	120 $\pm$ 11.3/78 $\pm$ 5.8
Background	38	0.74 $\pm$ 0.32	10.0 $\pm$ 1.96	131 $\pm$ 21.9/80 $\pm$ 9.6
Preproliferative	11	0.37 $\pm$ 0.2	8.9 $\pm$ 2.1	140 $\pm$ 17.3/87 $\pm$ 9.0
Proliferative	8	0.56 $\pm$ 0.27	9.4 $\pm$ 3.0	114 $\pm$ 24.4/85 $\pm$ 15.4
Photocoagulated	32	0.42 $\pm$ 0.14	10.1 $\pm$ 2.1	139 $\pm$ 23.9/82 $\pm$ 9.9

non-diabetics ($p < 0.005$). It will be noted from Fig. 2 that three subjects had retinal flow velocities greater than 1.2 mm/s; even if these subjects are excluded the results are still significant. In patients with preproliferative retinopathy retinal blood flow velocity was found to be 0.38 mm/s (± 0.2), a level significantly below that of patients with background retinopathy ($p < 0.0001$) and normal non-diabetics ($p < 0.05$). At the proliferative stage, flow velocity was found to be 0.56 mm/s (± 0.29), an increase which was not significant. In patients who had undergone photocoagulation (argon or xenon laser) retinal flow velocity fell to 0.42 mm/s (± 0.14), a level which was significantly below that of the patients with background retinopathy ($p < 0.0001$) and normal non-diabetics ($p < 0.02$).

Correlation studies were done on the two largest groups (background retinopathy and photocoagulation) to assess the influence on retinal blood flow of

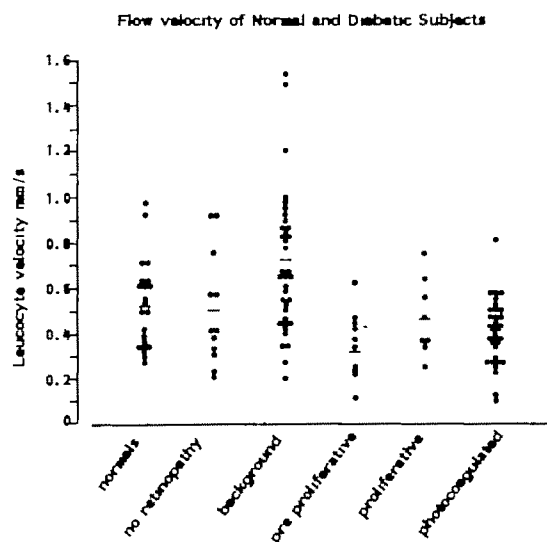


Fig. 2 Results of retinal flow studies in diabetics at different stages of retinopathy compared with those from a group of non-diabetic patients (see text).

pulse, blood pressure, blood sugar, and HbA1 levels. In those with background retinopathy there was no significant correlation with any of the parameters mentioned. In those patients who had undergone photocoagulation there was a significant negative correlation with diastolic blood pressure ($r = -0.423$, $p < 0.02$, $Y = 90.7 - 22.3 X$) where Y is diastolic blood pressure.

Discussion

Many investigators have looked at retinal blood flow in patients with diabetes mellitus. The technique generally used involves an intravenous bolus of fluorescein combined with serial photography, allowing density curves to be plotted for the dye in the superior temporal artery and vein. This allows a mean transit time to be calculated which, when combined with an estimate of the volume of the vascular bed (obtained from the diameter of major retinal blood vessels), gives an estimate of blood flow.² Other investigators^{3,4} have used a modification of this technique employing a two-point fluorophotometer which provides a continuous measurement of fluorescein density in artery and vein as opposed to the intermittent information provided by serial photographs. These methods suffer the disadvantage of being invasive, the fact that fluorescein leakage occurs at even the earliest stages of diabetes⁵ (introducing errors into the estimation of mean transit time), and that, with capillary closure, estimates of the volume of the vascular bed from the diameters of major retinal vessels may be unreliable. More recently Riva and colleagues^{6,7} have described a method of measuring retinal blood velocity in a non-invasive manner, employing a laser to measure the Doppler shift. This method is not yet widely available.

The blue-light entoptic phenomenon is used in this study as a measure of blood flow velocity in capillaries, an important advantage in studying a microvascular disease such as diabetes. However, certain warnings must be given. The technique simply measures velocity of leucocytes, so that if, for instance, the diameter of the vessels, including the capillaries increases, the change in leucocyte velocity alone may be a poor estimate of the increase in blood flow volume. The second problem is that flow velocity in macular capillaries only is measured, and this is not necessarily representative of all capillaries in the retina, especially in diabetic retinopathy, where capillary disease is widespread. It must also be emphasized that all measurements are subjective. However, reproducibility studies suggest that it is a reliable method of measurement.

Our group of normal persons gave a retinal flow

velocity of 0.54 mm/s, which differs from the result obtained by Riva and Petrig,¹ who found a speed of 0.7 mm/s. The difference between the two results may reflect the difference in the equipment used and possibly the smaller number of subjects in Riva and Petrig's group. This difference is not important so long as the same equipment is used throughout the study.

In the group of non-retinopathic patients the blood flow velocity was found to be very similar to that of normals. This is surprising, as it has been shown by other authors that in humans retinal blood flow is increased even in the early stages of diabetes.²³ Animal work⁴ has also shown that hyperglycaemia alone can increase retinal blood flow. Our failure to find any increase may be due to the inability of the method used to pick up small changes in flow velocity, or because capillary flow is not as variable as that of large vessels where all measurements prior to this technique have been taken. (Studies of flow at different blood sugar levels may clarify this.)

Our group of patients with background retinopathy showed a significant increase in flow velocity over normal non-diabetics and patients without retinopathy. This finding is in agreement with that of other investigators using different methods. The retina has a very high metabolic rate in non-diabetics,⁹ and the metabolic rate is increased in diabetes.^{10,11} An increased blood flow is therefore required.

At the preproliferative stage retinal blood flow velocity was found to be 50% of the value recorded in background retinopathy. Why such a marked reduction should occur is uncertain, as one might expect a reduction in size of the peripheral vascular bed to lead to an increase of flow through the macular area. The finding of reduced flow velocity in our study (admittedly in a small number of patients) could be explained on the basis of widespread generalised capillary occlusion leading to an increase in overall resistance in the vascular bed. On the assumption that perfusion pressure remains unchanged a reduction in flow should occur. It is also possible that a breakdown in autoregulation has occurred and the vessels can no longer dilate to compensate for the hypoxia.

Retinal flow velocity appeared to increase at the proliferative stage, though the increase was not

significant. After photocoagulation the flow velocity fell once more to the point where it was significantly below that of background diabetics but not significantly reduced from that of the proliferative stage. The finding of a reduced blood flow in photocoagulated patients as compared with that of patients with background retinopathy is in agreement with the findings from other authors working with both human and animal models.^{5,12,13}

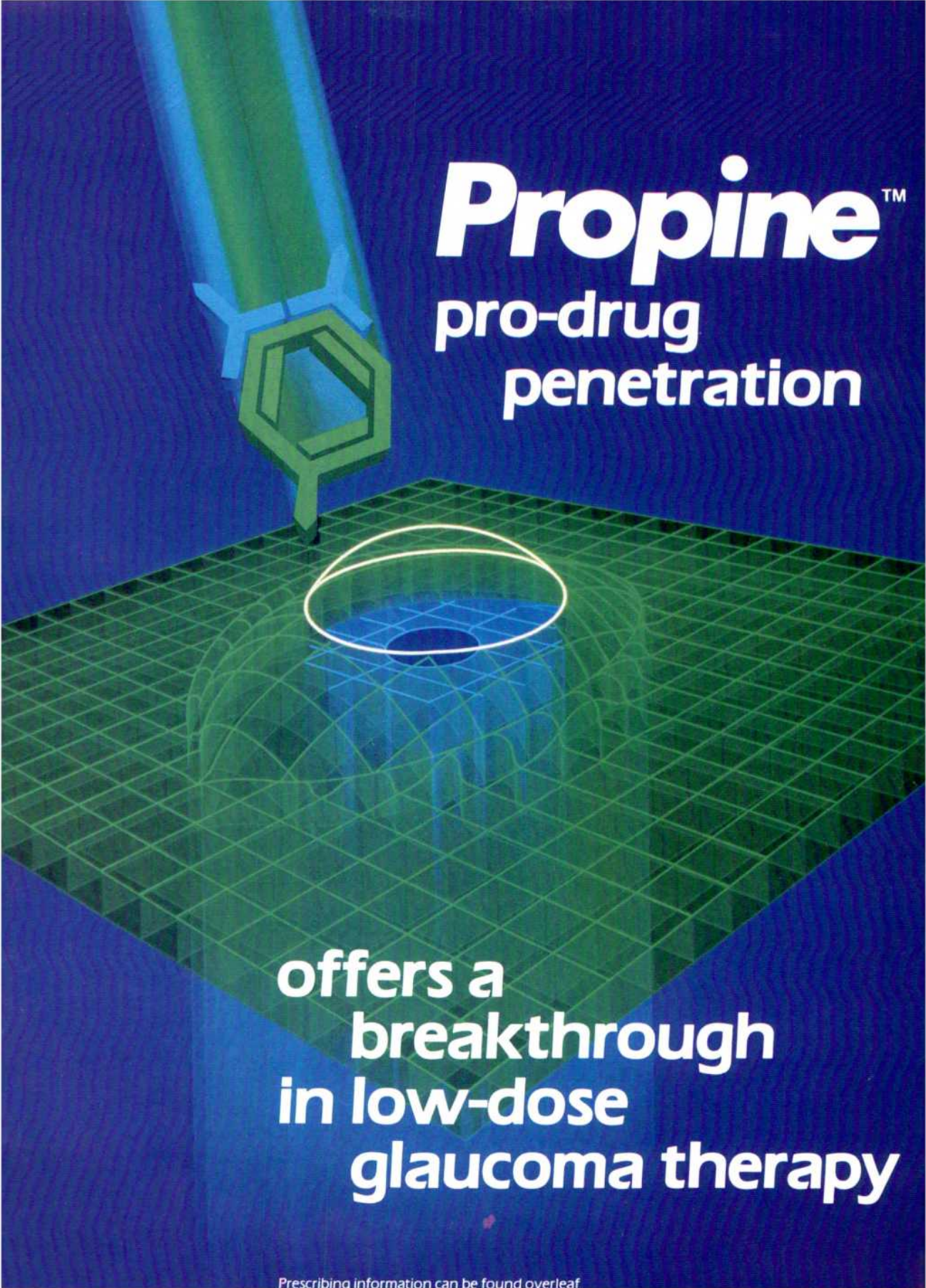
Photocoagulation results in reduction of the size of the vascular bed, destruction of the retina, and hence reduced metabolic demand. A reduction in blood flow could therefore be a result of the change in the vascular bed and/or an autoregulatory response to the reduced metabolic demand.

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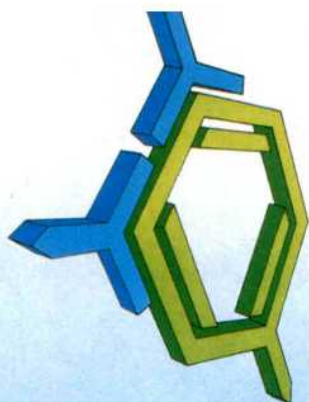


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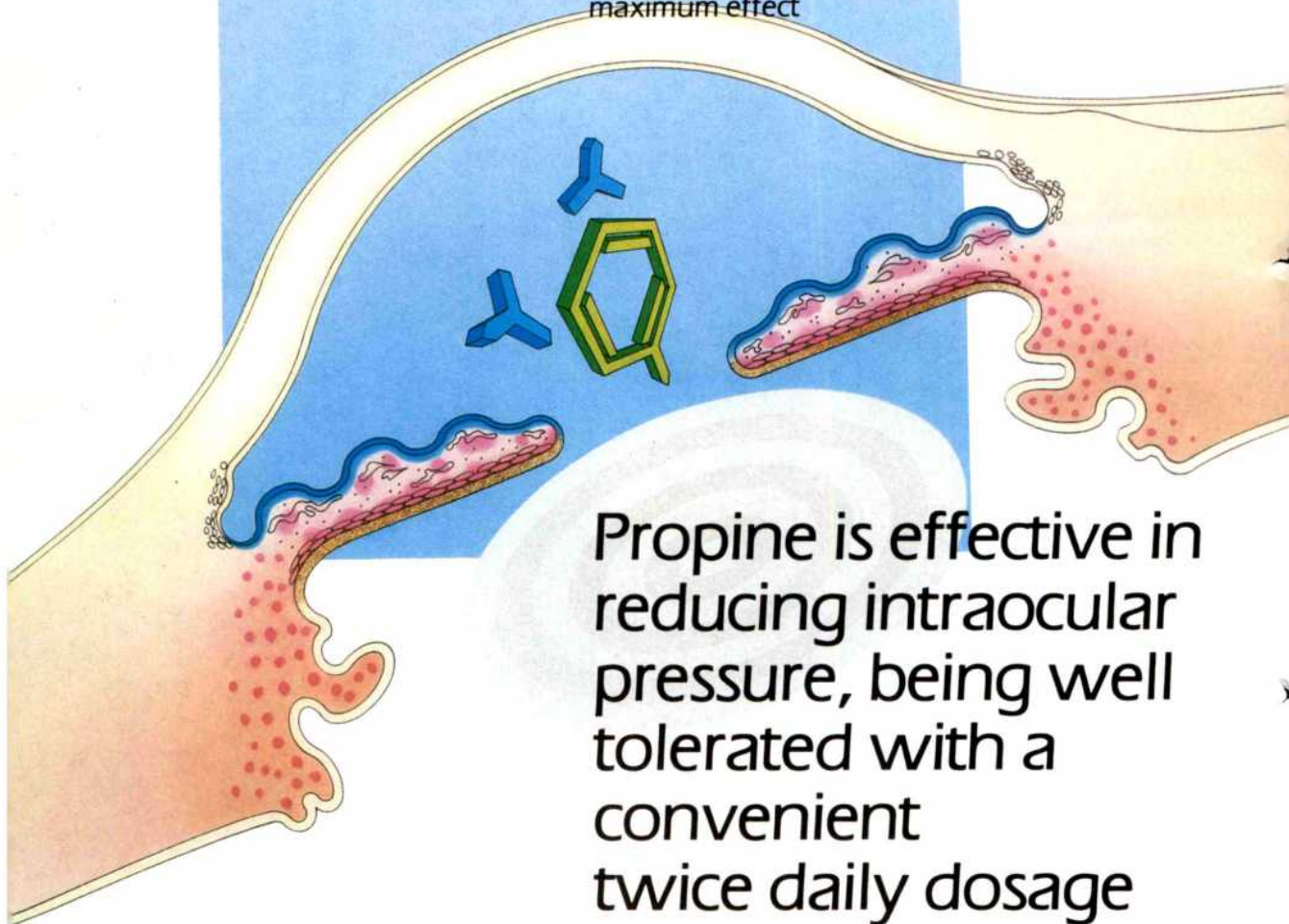
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Minnesota system corneal preservation

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SUMMARY The clinical and laboratory results with a modified Minnesota system of organ culture corneal preservation are presented. A refinement of our preservation technique using a closed system, as well as the addition of chondroitin sulphate to the medium is presented. Laboratory results show preservation of corneal endothelial integrity for at least 21 days with maintenance of normal corneal thickness. In addition, a 10-day quarantine system reduces the risk of donor contamination and secondary endophthalmitis. Preliminary results of the 34°C and 4°C closed Minnesota corneal preservation system using chondroitin sulphate show that it is safe and efficacious and allows intermediate to long-term maintenance of sterile thin tissue prior to corneal transplantation.

The success of penetrating keratoplasty in humans depends primarily on transplanting an adequate amount of viable donor endothelium.¹ Therefore any method used to store the donor cornea must maintain endothelial viability. Techniques for preservation of corneas prior to transplant currently include 4°C moist chamber refrigeration of the whole globe,² storage at 4°C in TC-199 with dextran (MK media),³ and cryopreservation.⁴ Each of these techniques, while serving a useful purpose, has significant limitations. A progressive loss of endothelial cells occurs at 4°C storage in both whole globe and MK storage techniques.^{2,5} This limits the duration of storage to less than 96 h.^{2,7} Cryopreservation allows a storage time of at least one year but it is a complex technology limited to a few centres and has a significant primary donor endothelial failure rate.^{4,8}

At the University of Minnesota we have been investigating 34°C organ culture of the cornea as a preservation technique since 1972 (Minnesota system) and have previously reported our results.⁹⁻²⁰ Although these studies confirm that human corneas can be successfully transplanted after five weeks of storage, three problems have limited the general acceptance of this method. First is the need to develop a system which assures sterility of donor tissue stored by this method. Secondly, the donor tissue thickens during storage, reducing the surgeon's

acceptance of this tissue. Thirdly, the standard organ culture method is technically complicated and expensive.

This paper reports our approach to solving the problems of sterility, thick donor tissue, and system complexity.

Materials and methods

For the past four years we have used a simpler closed system 34°C organ culture storage method. This system has significantly reduced complexity and expense and allows an adequate sterility check to be performed prior to transplantation. In this system corneas are suspended from a spinal needle inserted through the scleral rim in a 100-150 ml volume of medium and stored at 34°C for up to four weeks prior to transplantation without changing the medium. The current organ culture medium is shown in Table 1.

In one technique on day 1 the excised corneas are placed in 34°C open organ culture with gentamycin sulphate (90 µg/ml) as the only antibiotic present. On day 3 the corneas are transferred to another 34°C open organ culture without antibiotics, and on day 6 the corneas are suspended in the 34°C closed organ culture bottle (Fig. 1). In another technique the corneas are immediately placed in the closed system bottles. On day 5-7 of closed system storage 10 ml of the medium is removed from the bottle and plated for microbiological evaluation. The medium is evaluated for sterility under anaerobic conditions at 30°C and

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Table 1 *Minnesota system medium*

Minimum essential medium (Eagle's) with 25 mM HEPES buffer
Earle's salts without L-glutamine
L-glutamine—1% final concentration
Decomplemented calf serum (5% final concentration)
Fetal calf serum (5% final concentration)
1-5% chondroitin sulphate (50 000 MW)
90 µg/ml gentamicin sulphate

anaerobic conditions at 35°C. In addition, fungal cultures are done on Sabouraud's agar plates stored at 30°C. The bottles containing the corneas as well as the plates and media are examined daily for evidence of contamination. If after 7–10 days no growth is noted on any of the microbiological media, and the medium in the closed bottles containing the corneas is clear without pH change, the system is considered sterile and the corneas may be transplanted. For 4°C closed system storage the corneas are placed in 20–150 ml of media and then in a refrigerator to transplantation.

Fig. 1 *Cornea stored in the closed Minnesota system bottle.*

Laboratory and clinical evaluation

Studies were performed to evaluate the safety and efficacy of 34°C and 4°C closed Minnesota system organ culture. Clinical results were evaluated in regard to tissue sterility. Cat and human corneas were studied after preservation by ultrasonic pachymetry for corneal thickness, vital staining of the corneal endothelium with alizarin red S and trypan blue for cell maintenance, endothelial specular microscopy, and through primary transplantation. High molecular weight dextran (approx. 500 000 MW) and chondroitin sulphate (approx. 50 000 MW) were evaluated for their safety and efficacy in maintaining corneal deturgescence.

The first problem to be assessed was the ability of the closed system to allow reasonable assurance of donor tissue sterility. Between 1 January 1982 and 20 February 1984 over 400 organ culture corneas have been transplanted after 34°C Minnesota system storage. No cases of fungal or bacterial endophthalmitis have occurred since the new sterility routine has been in place.

The second problem of the original open system was thickening of corneal tissue during storage. Corneas may be thinned after 34°C Minnesota system storage by immersion of the cornea for 6–12 hours in a hyperosmotic solution such as in TC-199 with 5% dextran (MK medium). This, however, requires breaking the sterility quarantine prior to transplantation and may lead to endothelial cell loss. For this reason attempts were made to maintain corneal deturgescence during culture.

Initially high molecular weight dextran (500 000 MW) was used during organ culture in an attempt to maintain corneal deturgescence. Eight human corneas and 20 cat corneas stored for 21 to 28 days were examined after closed system organ culture using 1–5% high molecular weight dextran as an additive. The effectiveness of the corneal thinning was found to be proportional to the concentration of high molecular weight dextran. Concentrations of 5% dextran were found to be effective in maintaining corneal deturgescence in the cat and human cornea. Concentrations of high molecular weight dextran greater than 5% resulted in some precipitation of the dextran in the medium. Unfortunately, while dextran at concentrations of 5% yielded effective corneal deturgescence, the corneal endothelium showed extensive vacuolization of the cytoplasm and ingestion of the dextran on transmission electron microscopy (Fig. 2). At dextran concentrations as high as 8% areas of Descemet's membrane were devoid of endothelial cells, suggesting cell death. It was concluded that, while high molecular weight dextran at concentrations of approximately 5% were effective

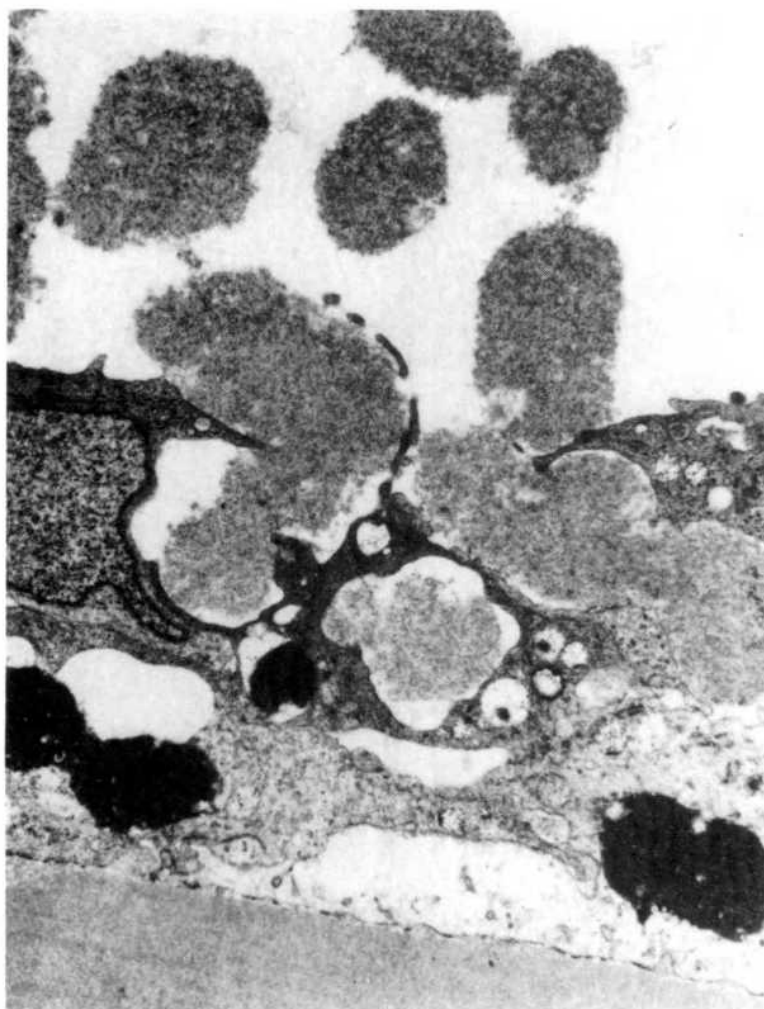


Fig. 2 Human corneal endothelium stored for four weeks in organ culture media containing 5% dextran shows significant dextran ingestion and vacuolisation on transmission electron microscopy. ($\times 15\,400$).

in maintaining corneal deturgescence, they may be toxic to the corneal endothelium during long-term corneal preservation at 34°C.

Several other substances, including mannitol, urea, glycerol, polyvinylpyrrolidone, and lower molecular weight dextrans were evaluated. None of these were found to be safe and effective during long-term corneal preservation.

Since 1982 the results of a technique using approximately 50 000 molecular weight chondroitin sulphate have been examined. A dose response curve for maintenance of corneal deturgescence in both cats and humans was evaluated in a range from 1% to 3.5% at 4°C on 34°C. In the human cornea a chondroitin sulphate concentration of 1.5% appeared to maintain normal corneal thickness dur-

ing preservation for 30 days (Fig. 3). In the cat cornea a concentration of 2.0–2.5% was required to maintain normal corneal thickness at 30 days, and this concentration was effective at 4°C and 34°C (Figs. 4 and 5).

Six cat corneas were then preserved for four weeks in 34°C closed system organ culture using 2% and 3% chondroitin sulphate, and they showed a normal endothelial mosaic by vital staining. Twelve more cat corneas were then transplanted after preservation in 34°C closed Minnesota system organ culture with chondroitin sulphate. Each transplant resulted in clear graft. Fig. 6 shows a clear transplant in a cat cornea and Fig. 7 the accompanying prestorage and postoperative central specular photomicrographs. The medium containing chondroitin sulphate has

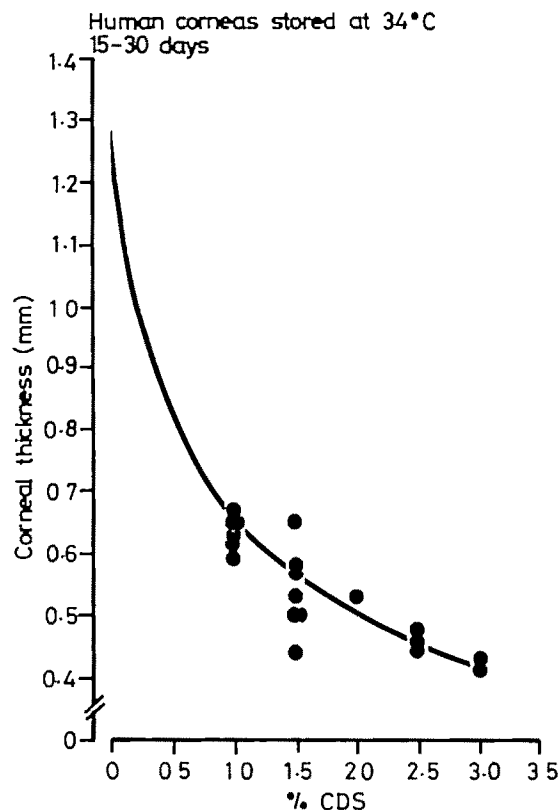


Fig. 3 Dose response curve for 50 000 MW medium containing chondroitin sulphate during 34°C Minnesota system storage of the human cornea for 15-30 days.

also been evaluated for corneal preservation at 4°C, and our preliminary studies show preservation of a normal appearing endothelial mosaic in the cat cornea for at least three weeks (Fig. 8) and in the human cornea for one week (Fig. 9).

So far 84 patients have received corneal transplants using corneas stored for 15-30 days in 34°C closed Minnesota system organ culture with chondroitin sulphate. Some corneal thickening has been noted in corneas stored over 14 days. Follow-up ranges from three weeks to one year. There have been no primary donor failures. Seven of the donor corneas have been evaluated through endothelial cell counts of the peripheral rim after trephination. After storage of 21-28 days the endothelial cell counts ranged from 2142 to 2666, with a mean of 2330 cells/mm². One patient has undergone postoperative specular microscopy centrally at six weeks, with an endothelial cell count of 2775 cells/mm² (Fig. 10). Evaluation of the donor rim endothelium in this patient following trephination also confirms excellent endothelial cell preservation (Fig. 10).

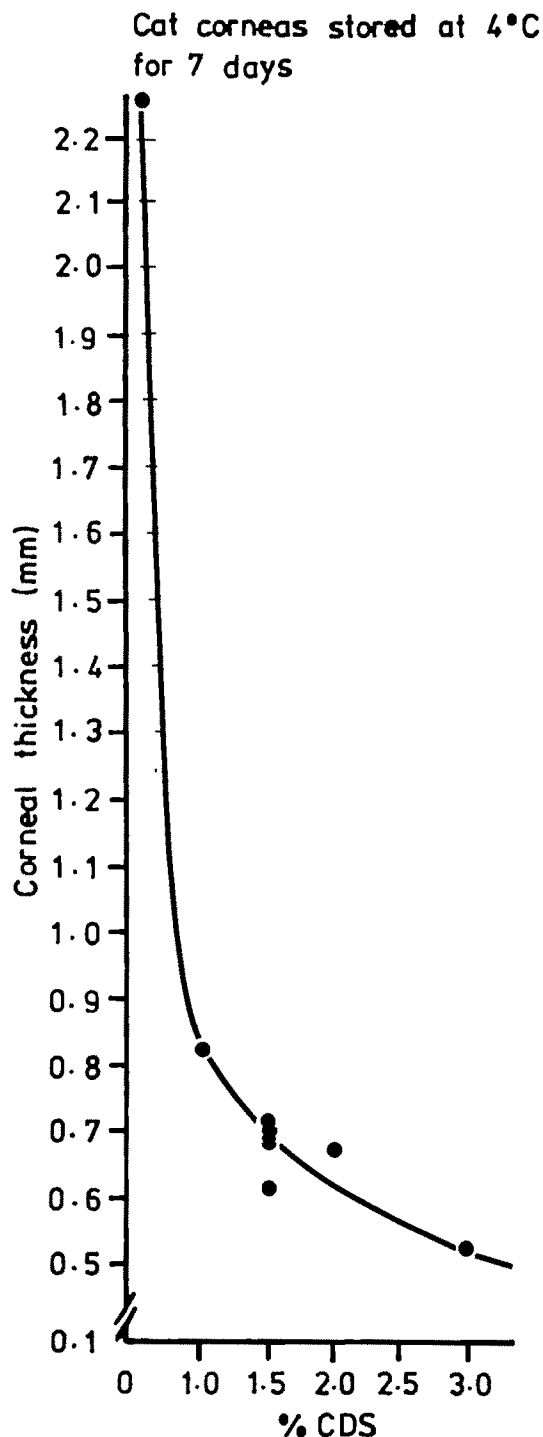


Fig. 4 Dose response curve for 50 000 MW medium containing chondroitin sulphate during 4°C Minnesota system storage of the cat cornea for seven days

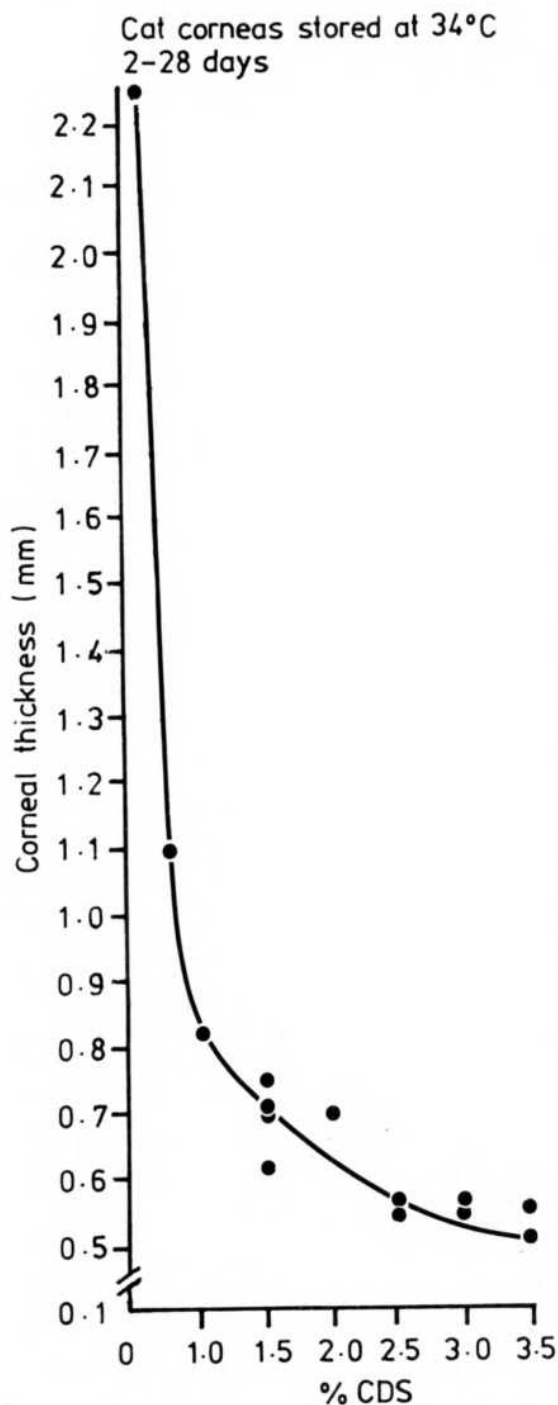


Fig. 5 Dose response curve for 50 000 MW medium containing chondroitin sulphate during 34°C Minnesota system storage of the cat cornea for 2-28 days.



Fig. 6 Postoperative appearance of a cat. Homograft three months postoperative using a cornea stored in 34°C closed Minnesota system with 2.5% chondroitin sulphate for 16 days.

Discussion

Our previous laboratory and clinical experience has convinced us that 34°C Minnesota system organ culture was a satisfactory technique for corneal preservation.⁹⁻²⁰ We have therefore increased our efforts to solve the three primary remaining problems, namely, sterility of the tissue, maintenance of corneal deturgescence during preservation, and simplification of the technique.

Since switching to the closed system with a two-week quarantine no cases of endophthalmitis have been noted in over 400 cases. The incidence of endophthalmitis following keratoplasty with MK stored tissue in one large study has been reported as 0.2%.²¹ While the incidence of endophthalmitis can never be reduced to zero, we consider that our results of over 400 keratoplasties with no care of graft contamination reassures us that this system provides satisfactory control of sterility.

The addition of chondroitin sulphate to the medium reduces the problem of corneal thickening during Minnesota system organ culture preservation at both 4°C and 34°C. This may allow the use of a single universal medium for storage of corneas from one to seven days at 4°C or as long as three to four weeks at 34°C with excellent endothelial preservation

Fig. 7 Prestorage and three month postoperative central corneal endothelial specular photomicrographs of the donor cornea in Fig. 5. The prestorage cell count is 2800 cells/mm² and the three month postoperative cell count is 2500 cells/mm.²

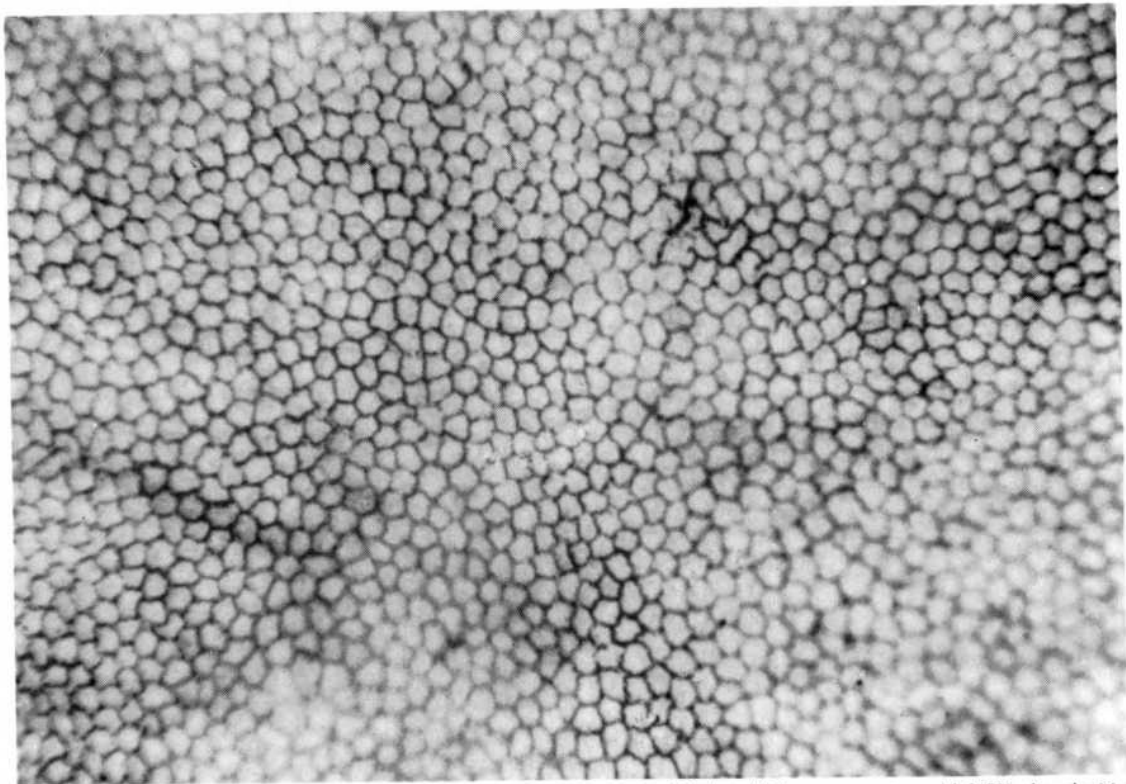
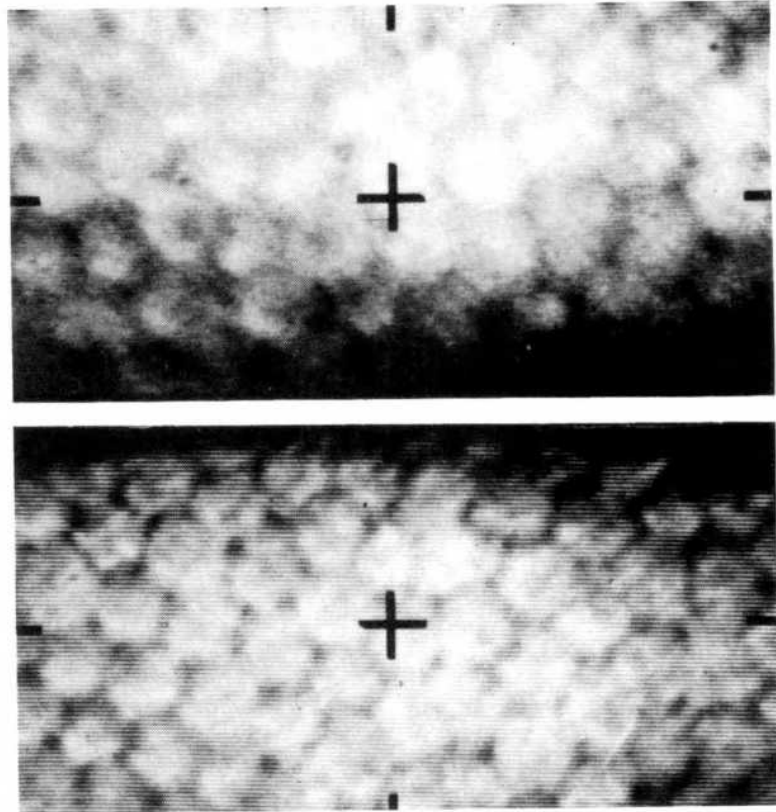


Fig. 8 Endothelial mosaic of the cat cornea after three weeks' storage in 4°C closed Minnesota system with 2.5% chondroitin sulphate.

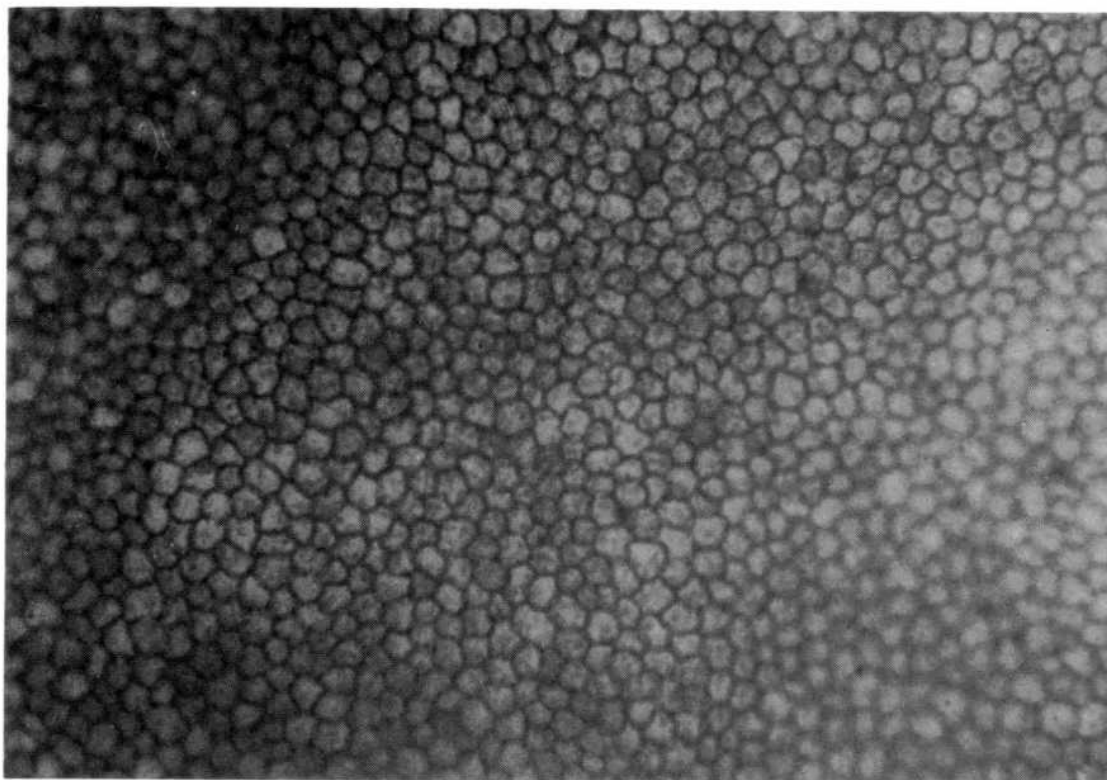


Fig. 9 Endothelial mosaic of the human cornea following seven days' storage in 4°C closed Minnesota system with 1.5% chondroitin sulphate.

and more normal corneal thickness. Use of this medium in the closed system also significantly simplifies the technique, reducing expense and complexity.

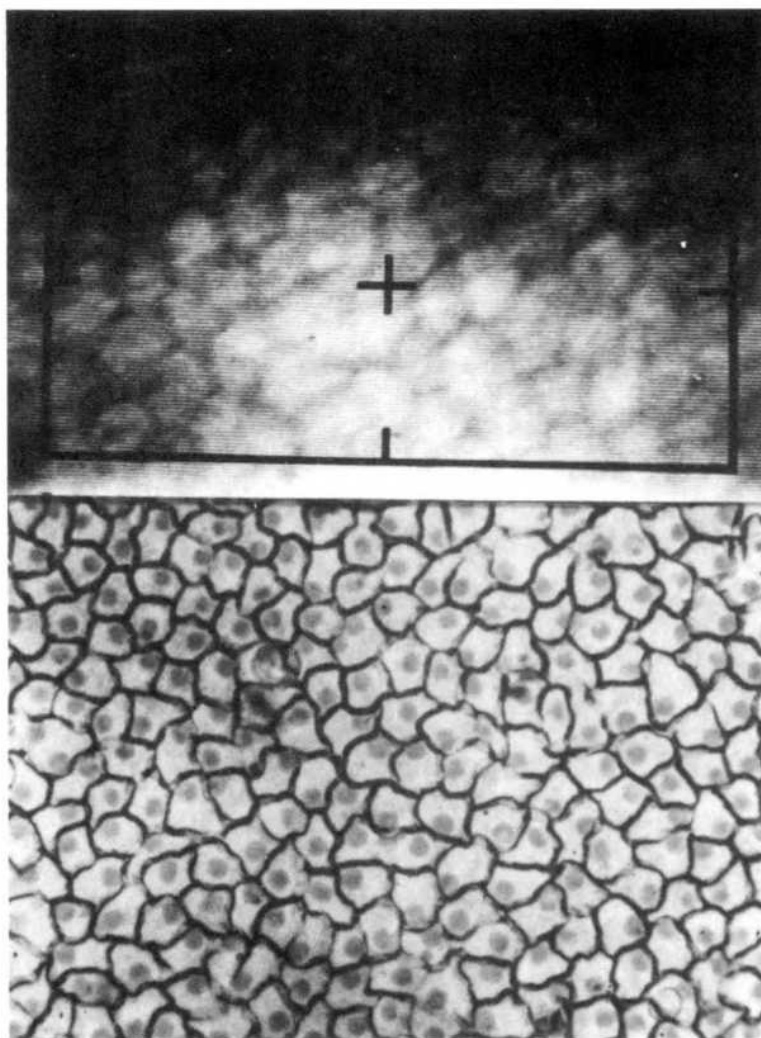
The results of this research indicate that 34°C and 4°C closed Minnesota system corneal preservation is safe and effective for intermediate term storage of donor corneas prior to human transplantation. The closed system allows a quarantine to ensure tissue sterility and simplifies the system. The addition of chondroitin sulphate to the medium provides a cornea of more normal thickness. We consider these improvements make the system more useful for corneal preservation. We are now continuing a careful prospective evaluation of endothelial viability and survival following penetrating keratoplasty.

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Fig. 10 Six week postoperative central corneal endothelial specular photomicrograph of a human donor cornea preserved in 34°C closed Minnesota system with 1.5% chondroitin sulphate for 15 days. The cell count is 2775 cells/mm.² Below is the endothelial mosaic of the donor rim after trephination.



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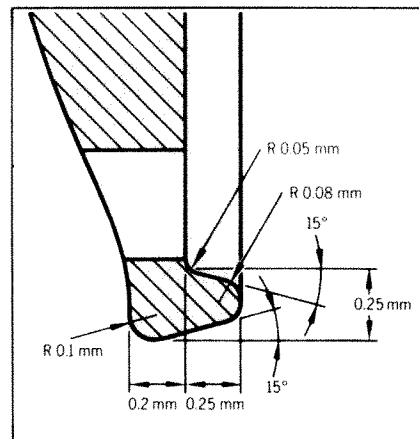
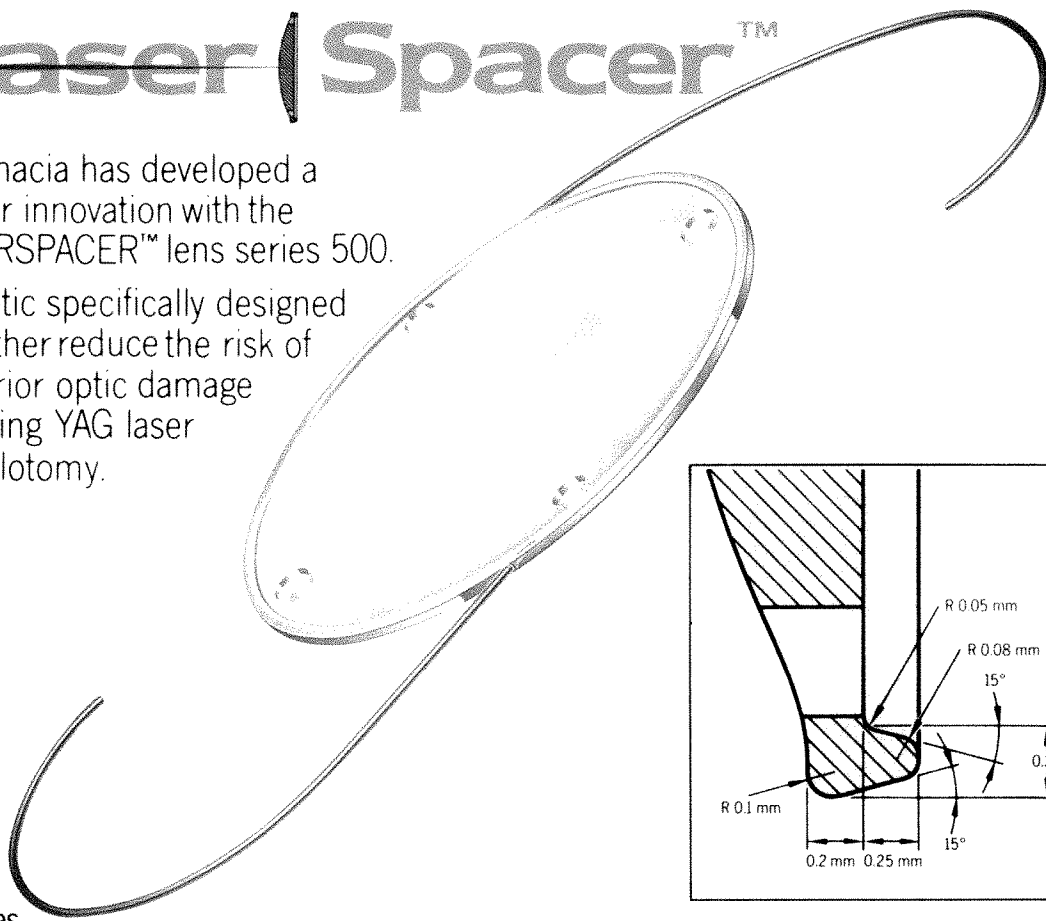
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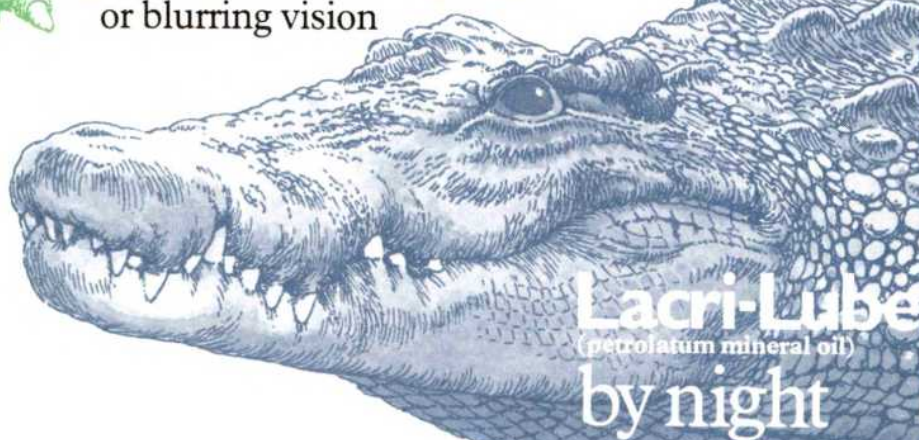
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Photokeratoscopy in fitting contact lens after penetrating keratoplasty

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SUMMARY The formula based on keratometric readings which is generally used is unsatisfactory for fitting contact lenses after penetrating keratoplasty, possibly owing to lack of information on the peripheral corneal toricity. In these studies a photokeratoscope was used to examine the entire graft topography. In all cases the corneal configuration became more normal after suture removal, but a considerable toricity still remained, especially near the graft-host junction. One month after removal of sutures spherical hard contact lenses (polymethylmethacrylate, PMMA) were fitted to 30 patients in accordance with data obtained by computerised analysis of the photokeratograms. Of the 30 patients (contact lens wearers) 27 (90%) obtained a stable vision of better than 20/30 for eight hours daily, and 24 (80%) achieved a stable vision of 20/20 for their full waking hours. After one year the contact lens wearers showed a significant decrease in the extent of astigmatism when compared with the non-contact-lens wearers (10 patients). These results suggest that the photokeratoscope can be more useful than ordinary keratometers in fitting contact lenses after keratoplasty, and that hard contact lenses have moulding effects on the graft topography.

Improvements in surgical techniques and postoperative care have resulted in a higher rate of clear grafts after penetrating keratoplasty. However, there are a considerable number of cases with a high degree of corneal astigmatism and ametropia, which prevent good vision. Although surgeons attempt to obtain emmetropic anastigmatic transplants, no reliable reproducible techniques have yet been established.¹⁻⁵

Because most postkeratoplasty patients have some degree of corneal irregular astigmatism, contact lenses, especially hard contact lenses, are required for satisfactory visual rehabilitation.⁶ However, conventional methods for fitting contact lenses, based on keratometric readings, do not apply to these patients.⁷ Ordinary keratometers provide only measurements of the apical corneal curvatures approximately 2 mm from the visual axis, while a higher degree of toricity is often present near the host-graft junction. To obtain successful results good

relationships between a lens and the central and peripheral cornea are of great importance. Therefore it can be said that the lack of information on the peripheral corneal toricity may be closely related to difficulties in fitting contact lenses after keratoplasty.

In this study the entire corneal topography was examined with a photokeratoscope, and hard contact lenses were fitted in accordance with the data obtained by computerised analysis of the photokeratograms.⁸

Patients and methods

Forty patients with unilateral phakic corneal transplants were studied. The preoperative diagnoses of these patients included keratoconus (25 eyes), herpes simplex stromal keratitis (8 eyes), and leucoma of unknown aetiology (7 eyes). None had evidence of retinal diseases, including age-related macular degeneration and clinically significant cystoid macular oedema. The ages of the patients ranged from 15 to 75 years (mean 47 years). Hard contact lenses (polymethylmethacrylate, PMMA) were fitted to 30 patients (contact lens wearers), while lenses were not prescribed for the other 10 patients (non-

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contact-lens wearers) because they could not manipulate the lenses owing to poor dexterity. The latter group were used as controls in a study of the effect of contact lens wear on postkeratoplasty astigmatism.

All keratoplasties were performed by one surgeon (RM) under local anaesthesia. The corneal button was removed from the epithelial side with a trephine (7 to 8.5 mm in diameter) and secured in place with eight interrupted 9-0 virgin silk sutures followed by a single 10-0 nylon monofilament running suture.^{9,10} After reformation of the anterior chamber of the eye with a balanced salt solution, the interrupted sutures were removed. The running suture was removed six to 12 months (mean 10 months) postoperatively. All corneas were serially examined with a photokeratoscope (SUN PKS-1000) which measures the entire corneal topography (Fig. 1). The photokeratograms obtained were subjected to a computerised analysing system⁸ that calculated the entire corneal configura-

tion as well as the keratometric readings¹¹ (Figs. 2 and 3, middle). In the corneas where the mire images were out of focus owing to highly irregular or extensive curvatures the midpoint of the blurred mire images was analysed to calculate the average keratometric readings.

Contact lenses were fitted in accordance with the data obtained by photokeratoscopy and refraction of the eye. This procedure was done at one month after suture removal, during which the corneal epithelial defects associated with the suture removal were completely healed in all the cases studied. Spherical contact lenses with a diameter of at least 1 mm larger than the grafts were fitted in order to minimise damage to the host-graft junction. An acceptable fit was considered to be a lens with good centration and an adequate movement (1 to 2 mm) during blinking to obtain proper tear exchange under the lens. The proper tear exchange was designated as a washout of fluorescein occurring in less than five minutes. The

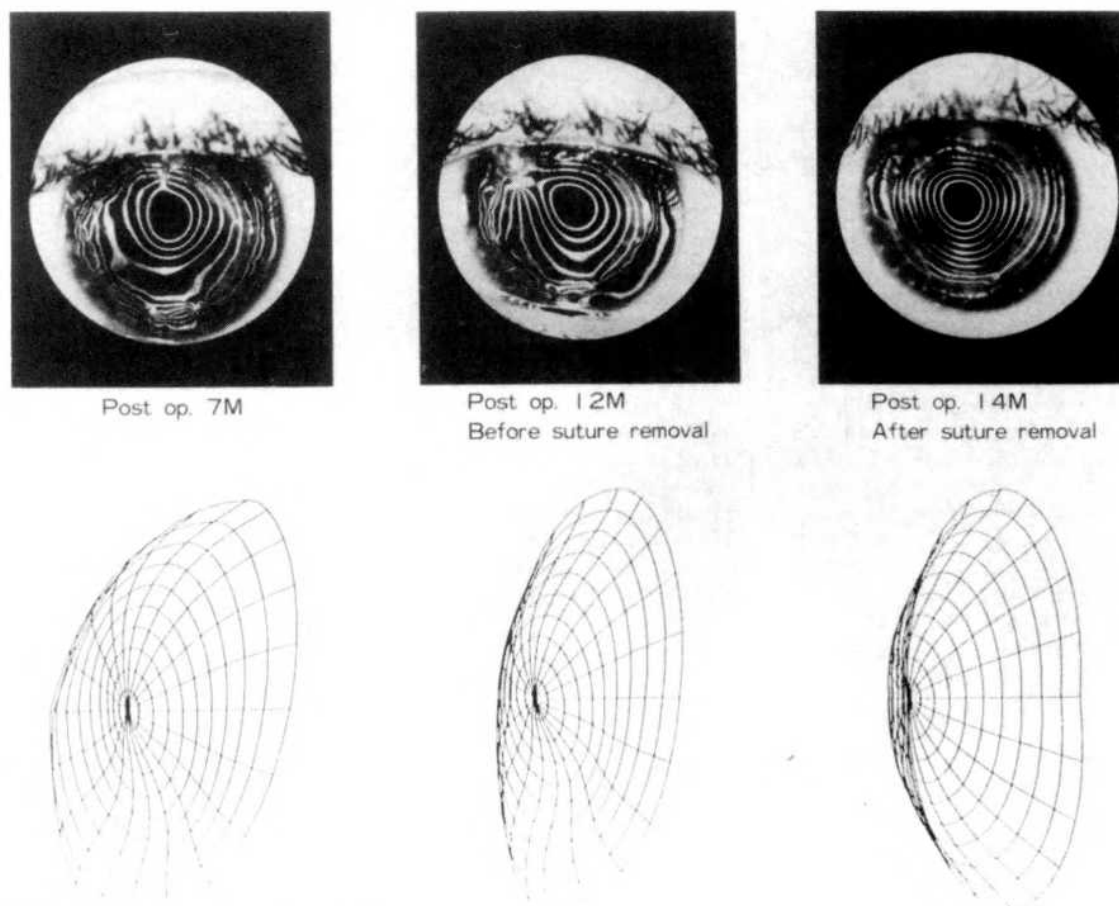


Fig. 1 Sequential photokeratograms after penetrating keratoplasty.

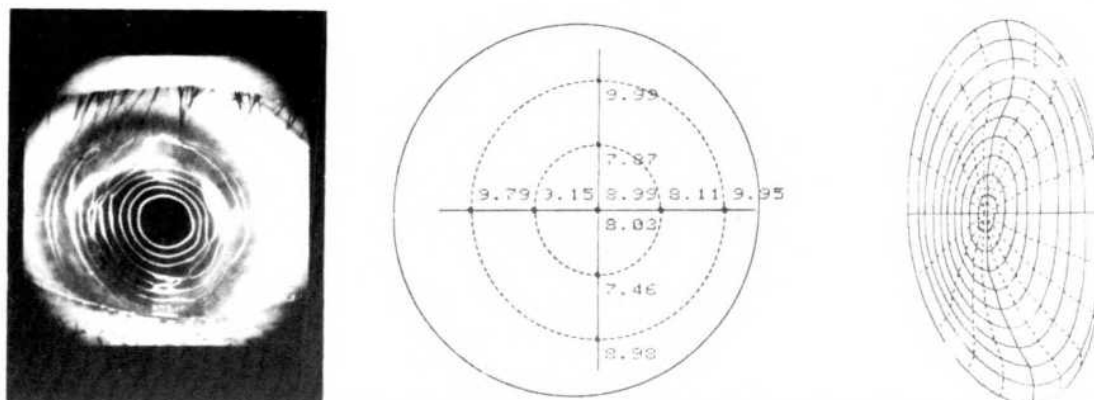


Fig. 2 The corneal topography in a 41-year-old male with herpes stromal keratitis who underwent keratoplasty with an 8 mm corneal button. Each number in the middle figure represents the radius (mm) of the curvature for the respective region of the cornea, which provided quantitative parameters to fit a lens.

peripheral posterior curve of the lens was modified according to the peripheral corneal toricity, if needed, in order to obtain a better lens-cornea relationship.

Results

In all the cases studied the corneal topography was quite flat and irregular during the early period after penetrating keratoplasty (Fig. 1, left), but it became steeper and more regular with time (Fig. 1, middle). Suture removal resulted in sudden changes in the graft topography (Fig. 1, middle and right). There was considerable individual variation in the degree of these topographic changes. After suture removal the configuration of the central cornea became more spherical, but a considerable toricity still remained, especially near the host-graft junction (Fig. 1, right).

Fig. 2 shows the corneal topography in a 41-year-old male with herpes stromal keratitis who underwent keratoplasty with an 8 mm corneal button. Because the cornea had flatter than normal central and peripheral curvatures¹² (Fig. 2, middle), a lens with a diameter of 9.2 mm and a central posterior (base) curve of 8.65 mm was fitted, and the peripheral posterior curve of the lens was modified to be flatter. This patient has been wearing the lens for his full waking hours with a stable vision of 20/20.

Fig. 3 shows the corneal topography in a 24-year-old female with keratoconus undergoing keratoplasty with a 7.5 mm graft. Because the cornea had steeper than normal central curvatures and flatter than normal peripheral curvatures¹² (Fig. 3, middle), a lens with a diameter of 9.5 mm and a base curve of 7.35 mm was fitted and the peripheral posterior curve of the lens was also modified to be flatter. The patient

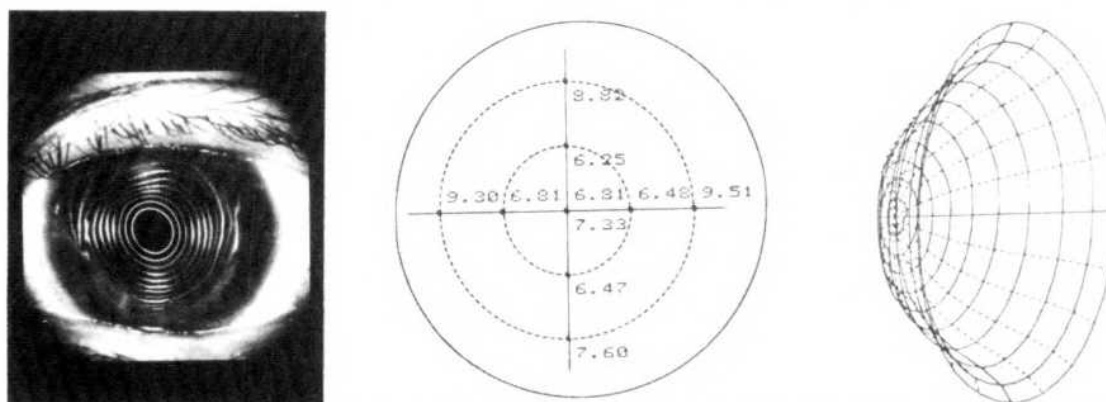


Fig. 3 The corneal topography in a 24-year-old female with keratoconus who underwent keratoplasty with a 7.5 mm graft. Each number in the middle figure represents the radius (mm) of the curvature for the respective region of the cornea, which provided quantitative parameters to design a lens.

Table 1 *Changes in corneal astigmatism*

Contact lens wear	Average astigmatism (dioptres)			
	0*	3 months	6 months	12 months
Yes (n=30)	4.5	2.7	2.5	2.2
No (n=10)	4.2	4.0	3.8	3.5
	NS	NS	NS	p<0.05

*Corresponds to one month after suture removal

NS=not significant (Student's *t* test)

has worn the lens for 10 hours a day with a stable vision of 20/20.

With contact lens correction alone 27 (90%) of the 30 patients obtained a stable vision of better than 20/30 for eight hours a day, and 24 (80%) obtained a stable vision of 20/20 for their full waking hours. Only three patients could not obtain either more than eight hours' lens wear or a stable vision of better than 20/30. All of them had an astigmatism of greater than 6 dioptres (D).

So far as the lens fitting and complications were concerned, a small number of problems were observed. Inadequate centration and/or movement of the lens was noted in three patients (10%), all of whom had a greater than 6 D astigmatism and also showed an excessive attraction of the lens for the cornea. Three patients (10%) had an air bubble under the lens, which did not interfere with tear exchange or obscure vision. Six patients (20%) showed a slight degree of ocular congestion, and 4 (13.3%) occasionally developed a mild degree of fluorescein staining of the corneal epithelium. None of these complications resulted in discontinuing the use of the lens.

The average astigmatism prior to contact lens wear (one month after suture removal) was 4.5 D for the contact lens wearers and 4.2 D for the non-contact-lens wearers respectively (Table 1). There was no significant difference between these values. The non-contact-lens wearers showed a gradual decrease in the astigmatism during the one year follow-up. This decrease, however, was not statistically significant. By comparison, the contact lens wearers showed a marked decrease in the astigmatism to 2.7 D during the first three months and a gradual decrease thereafter. After one year the average astigmatism for the contact lens wearers (2.2 D) was significantly smaller ($p<0.05$) than that for the non-contact-lens wearers (3.5 D; Student's *t* test).

Discussion

Even if carried out by skilled surgeons with modern techniques most corneal grafts result in some degree of ametropia and irregular astigmatism,¹⁻³ and con-

tact lenses are often required for satisfactory correction of vision.^{4,7} Because of the variation in the extent of corneal toricities from patient to patient, fitting contact lenses after keratoplasty is usually made by trial and error. The fitters must be skilled to modify the parameters of the lens to effect proper centration, venting, and movement, and many lenses with various base curves and diameters may need to be tried.⁶ Most of these tedious procedures could be attributed to incomplete information on the entire graft topography, since ordinary keratometers provide only the central curvatures approximately 2 mm from the visual axis.

In contrast the photokeratoscope used in this study has the advantage of permitting examination of the entire corneal topography, which has been shown to be more useful than ordinary keratometers in fitting contact lenses in patients with some degree of refractive error⁸ and those with keratoconus.^{13,14} Our study showed that this instrument can also be useful in fitting contact lenses after penetrating keratoplasty.

Our serial observations on the graft topography showed that, although the central corneal configuration becomes more normal after suture removal, a considerable toricity still remains, particularly in the peripheral cornea. This aspect appeared to be significantly related to the difficulties in the fitting, because most of our cases required modification of the peripheral posterior curves of the lens to obtain good centration and an adequate lens-cornea relationship. These modifications, however, were made easily from the photokeratographic data for the peripheral corneal toricity.

All the lenses used in this study were larger than the grafts. Lenses smaller than the grafts can be fitted, but because of their small size they are usually uncomfortable and unstable, causing fluctuating vision and possible damage to the host-graft junction.⁶ In order to stabilise such smaller lenses, steepening the base curve is often required, which would increase the attraction of the lens for the cornea, resulting in intolerance of the lens after several hours of lens wear. By comparison larger lenses may decrease the damage to the host-graft junction^{6,7} and offer good centration and movement, and they may provide a stable vision and a proper venting which facilitates oxygen exchange under the lens.⁷ Contact with the upper lid can also help to provide good stabilisation and movement of the lens.

Despite the satisfactory results in most of our series, three patients with an astigmatism of greater than 6 D did not obtain a vision of better than 20/30 and did not tolerate the lens for more than eight hours a day. Such patients would require toric lenses rather than spherical ones⁶ or could be considered for

refractive surgery, such as relaxing incisions or wedge resection.¹⁵

As reported previously,^{6, 16, 17} we found that the graft topography is in a state of transition for several months after suture removal. We also found prospectively that the contact lens wearers have a significant decrease in the extent of corneal astigmatism after one year of lens wear when compared with the non-contact-lens wearers. A similar observation has been made in a retrospective study by Ruben and Colebrook.¹⁷ These findings indicate that contact lenses have a moulding effect on the graft topography.^{6, 17}

We thank Mr Etsuji Adachi (SUN Contact Lens Co. Ltd., Kyoto, Japan) for his valuable technical assistance in this study.

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Complement activation in uveitis

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SUMMARY To determine whether complement is activated in uveitis we have measured plasma levels of C3d, a sensitive indicator of complement activation. Increased levels of C3d were found in 11 of 15 patients with idiopathic uveitis, 13 of whom had circulating immune complexes containing complement components. Since during complement activation potent mediators of inflammation are generated, it is suggested that the activation of complement, possibly triggered by uveal deposition of immune complexes, has an important role in the pathogenesis of uveitis.

The pathogenesis of uveitis has not yet been established, but clinical and experimental data strongly implicate immune mechanisms.¹⁻⁴ The condition may be associated with connective tissue disorders such as juvenile rheumatoid arthritis, ankylosing spondylitis, and, though rarely, systemic lupus erythematosus,^{2,4} where immune complexes are thought to have a pathogenetic role.⁵ Circulating immune complexes have also been found in patients in whom uveitis is the only detectable lesion.⁶ Circulating immune complexes, however, might also represent an immune reaction secondary to ocular tissue destruction. A primary role for immune complexes in the pathogenesis of uveitis is suggested by the evidence obtained in experimental animal models.⁷⁻⁹ Wong *et al.*¹⁰ have shown that the administration of heterologous serum to rabbits previously sensitised with the same serum produces uveitis which becomes progressively more serious at every subsequent injection, suggesting that the increasing levels of immune complexes are closely related to the eye injury. Furthermore an increase in vascular permeability, a typical sign of chronic uveitis, can be reproduced in experimental animals by the direct administration of preformed immune complexes.⁹ In experimental models of lens induced uveitis the

deposition of immunoglobulin and complement factors has been detected by immunofluorescence,¹¹ suggesting complement fixation by deposited immune complexes.

So far no study on complement activation in uveitis in man has been performed in spite of the fact that circulating immune complexes and hypocomplementaemia have been repeatedly reported in this condition.¹⁴⁻¹⁶ We therefore decided to investigate complement activation occurring in vivo in such patients by measuring plasma levels of C3d, a fragment derived from the activation of C3. Simultaneously we have investigated the presence and composition of circulating immune complexes, titres of autoantibodies, and immunoglobulin levels.

Patients and methods

PATIENTS

Fifteen patients suffering from idiopathic uveitis were studied: seven (four females, three males, age range 14-64, median 53 years) had anterior uveitis (chronic iridocyclitis), and eight (six females, two males, age range 18-68, median 54 years) had chronic panuveitis. Thirteen patients had symptoms for over six months, while two patients with iridocyclitis had had symptoms for three to six months. Six patients were on systemic corticosteroid treatment (prednisone 10-30 mg daily).

Thirty-nine normal controls, 19 males and 20 females with an age range of 10 to 70 years, median 48 years, were also studied.

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Table 1 Analysis of immune complex composition after PEG precipitation in 15 patients with chronic panuveitis (P) or iridocyclitis (I)

Patient no	Sex	Age	Diagnosis	IgG	IgM	IgA	C3	C4	Clq
1	M	43	P	+	-	-	++	++	+
2	F	65	P	++	-	+	++	++	+
3	F	61	P	++	-	-	-	+	-
4	F	47	P	++	+	+	+	+	+
5	M	68	P	+	-	+	-	+	+
6	F	18	P	++	-	-	-	+	-
7	F	38	P	-	-	-	-	-	-
8	F	66	P	-	-	-	-	-	-
9	F	14	I	++	+	-	++	++	+
10	F	57	I	+	-	-	-	-	+
11	M	64	I	++	+	-	++	++	+
12	F	49	I	++	-	-	-	-	-
13	M	55	I	++	-	-	-	-	+
14	M	53	I	++	-	-	-	+	-
15	F	25	I	++	-	-	-	-	-

METHODS

Serum was obtained by centrifuging clotted blood at 1000 g. Plasma was separated immediately after drawing blood in edetic acid (EDTA) (10 mmol/l). Samples were stored at -70°C till tested.

C3d was measured by a recently described nephelometric technique¹⁵ using commercially available anti-C3d antiserum (DAKO). Immune complex analysis¹⁶: to separate immune complexes 200 μl of serum was mixed with 200 μl of 4% polyethylene-glycol (PEG) 6000 dissolved in borate buffer (pH 7.4, 0.1 mol/l). This mixture containing 2% PEG was incubated at 4°C for 60 minutes and then centrifuged at 4°C for 20 minutes at 1500 g. The supernatant was discarded and the precipitate was resuspended in 50 μl of borate buffer and analysed by means of bidimensional immunodiffusion. Specific antisera directed to IgG, IgM, IgA, and complement factors C3, C4, Clq were used (Behring). Owing to the semiquantitative nature of this technique, immune precipitates are reported in Table 1 as absent (-), detectable (+), or heavy (++).

Serum levels of immunoglobulin G, A, M and of complement factors C3 and C4 were measured by a standard nephelometric technique.¹⁷ Non-organ-specific autoantibodies and IgM rheumatoid factor were measured by standard techniques.¹⁸ Statistical analysis was by Student's *t* test and χ^2 .

Results

Eleven out of 15 (73%) patients had increased levels of C3d. The mean of the patients' values was significantly higher (1.0 ± 0.1 , mean $\pm$ SEM) than that of the controls (0.499 ± 0.017 ; $t=7.3$, $p<0.001$) (Fig. 1). Circulating immune complexes were detected in 13 out of 15 patients, and details on their composition are summarised in Table 1. IgG could be detected in

13 of the 15 precipitates (87%) but IgM in only three cases (20%) and IgA in three cases (20%). C3 was found in five of 15 precipitates (33%), C4 in nine out of 15 (60%), and Clq in nine out of 15 (60%).

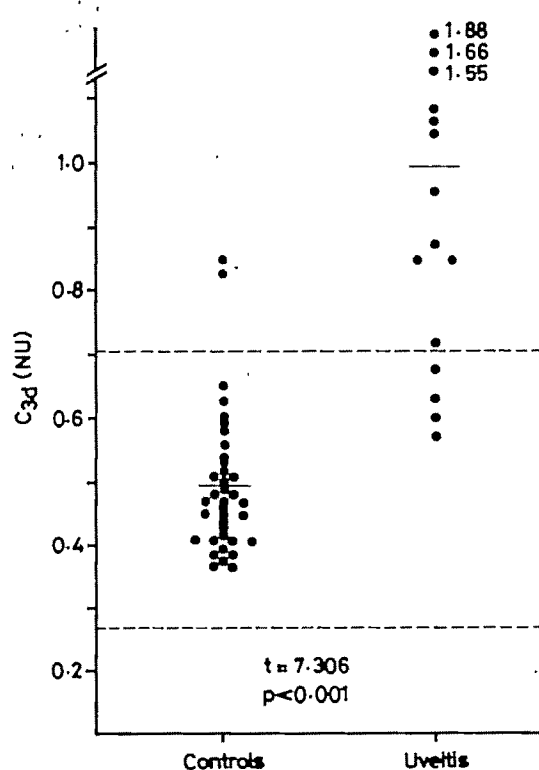


Fig. 1 C3d plasma levels in patients with uveitis and in normal controls. C3d values are expressed in nephelometric units (NU). The dotted lines represent the upper and lower limit of normal obtained as 2SD above and below the mean of results in controls.

Table 2 Blood level of immunoglobulin G, A, M, complement factors C3 and C4, fragment C3d, and titres of rheumatoid factor (RF) and autoantibodies (AA) in the 15 patients with chronic uveitis

Patient no.	IgG g/l	IgA g/l	IgM g/l	C3 g/l	C4 g/l	C3d NU*	RF	AA
1	10.5	2.7	1.2	0.90	0.24	1.10	—	—
2	13.8	2.4	0.3	1.00	0.35	0.85	—	1:10†
3	20.6	2.5	0.4	1.15	0.37	0.72	1.10	—
4	13.9	3.0	2.4	1.11	0.31	1.55	—	—
5	13.4	1.5	0.6	0.86	0.49	1.88	—	—
6	8.6	2.0	0.7	0.89	0.39	0.96	—	—
7	8.9	1.6	1.3	0.66	0.30	0.68	—	—
8	7.4	1.4	1.4	0.72	0.32	0.85	—	—
9	11.8	1.1	1.3	0.78	0.26	0.57	—	1:10‡
10	11.8	2.9	2.5	0.88	0.26	1.66	—	1:10‡
11	15.7	3.4	2.4	0.96	0.33	0.60	—	—
12	12.0	1.7	1.5	0.86	0.25	1.07	—	—
13	9.7	1.5	0.7	0.65	0.21	1.05	—	1:10†
14	6.0	1.1	0.6	0.74	0.39	0.88	—	—
15	3.7	0.5	0.6	0.41	0.10	0.63	—	—

Normal values = IgG: 5–16 g/l, IgA: 0.5–4 g/l, IgM: 0.5–2 g/l, C3: 0.5–1.2 g/l, C4: 0.2–0.4 g/l, C3d <0.71 NU.

*NU = nephelometric units

†GPC = gastric parietal cell autoantibody.

‡ANA = antinuclear autoantibody

Increased blood levels of C3d were significantly associated with presence of circulating immune complexes containing IgG ($\chi^2=24.5$, $p<0.0005$). Serum levels of immunoglobulins G, A, and M and of the complement factors C3 and C4 were normal in the great majority of cases (Table 2). Non-organ-specific autoantibodies and rheumatoid factor were present in five patients (33%) (Table 2). The findings were not significantly different in treated and untreated patients.

Discussion

Our data confirm the presence of circulating immune complexes in patients with idiopathic uveitis. Analysis of their composition has produced the interesting observation that in addition to immunoglobulin they contain complement components of the classical pathway. This suggests that they are able to fix complement in vivo. Complement-fixing immune complexes have been shown to play a pathogenetic role in other conditions such as experimental glomerulonephritis, where antigen, antibody, and complement factors are found deposited in a typical pattern in injured glomeruli.¹⁹ A similar pattern of immunoglobulin and complement deposition is found in renal biopsies of patients affected by a variety of glomerulonephritides, suggesting similar damaging mechanisms.²⁰ Although the high morbidity and the technical difficulty associated with uveal biopsy prevent a direct detection of tissue immune reactants in man, animal studies have shown eye deposition of immunoglobulin and complement in experimentally induced uveitis.¹¹ Furthermore

complement depletion has been shown to prevent both experimental uveitis and glomerulonephritis.^{21,22}

In the present study we show that IgG-containing circulating immune complexes in patients with uveitis are significantly associated with increased levels of C3d, a sensitive indicator of complement activation. This is not surprising, since immunoglobulin G belonging to IgG1, IgG3, and, to a lesser extent, IgG2 subclasses activate complement when combined with their antigen. During complement activation a series of potent mediators of inflammation are produced.²³ It is thus possible that they are responsible for the phlogistic ocular lesion.

Why the inflammatory process is confined to the eye remains to be established. Deposition of immune complexes has been shown to be influenced by the class of immunoglobulin, the antigen-antibody ratio, antigen adhesiveness, and organ vascularisation.⁴ The eye shares with the kidney the ability to filter large amounts of fluid. This plus a specific affinity of immune complexes for the uvea could explain the localisation. Recently, Lowder *et al.* have shown that C3b and Fc receptors are present in capillaries and along the basement membrane of the ciliary body.²⁴ It is thus possible that uveitis results from the binding of circulating immune complexes for which the uveal tract has appropriate receptors.

The finding of normal serum C3 and C4 but increased C3d in uveitis may reflect a phenomenon similar to that found in rheumatoid arthritis.²⁵ In this condition normal C3 and C4 levels in the serum contrast with reduced levels in the affected joints, while C3d, increased in the serum, show an even

higher level in the joints: a similar gradient of concentration may occur in uveitis. To determine more directly a possible pathogenetic role of complement-activating immune complexes in uveitis, the presence of immune complexes and complement fragments should be sought in the aqueous humour.

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Primary vitreoretinal dysplasia resembling Norrie's disease in a female: association with X autosome chromosomal translocation

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SUMMARY A female infant with the typical clinical and histopathological features of vitreoretinal dysplasia is described. She had an apparently balanced reciprocal chromosomal translocation 46XX,t(X;10) with the X chromosome breakpoint being on the short arm. Since the parents' karyotypes were normal, it is most plausible that a de novo chromosomal translocation disrupted the vitreoretinal dysplasia gene itself. The severe clinical symptoms of this heterozygous female patient were explained by non-random X inactivation. She may have had Norrie's disease, an X linked recessive disorder due to an X autosome translocation.

Vitreoretinal dysplasia is induced by an arrest in the development of the vitreous and retina due to either genetic or environmental factors. Aetiologically heterogeneous diseases frequently present morphological similarities in their clinical and histopathological features. Congenital pseudoglioma, non-attachment of the retina, and falciform folds of the retina among others are terms used to describe the clinical picture, and the histopathological abnormalities, usually designated as retinal dysplasia, include the formation of rosettes in the dysplastic retina and proliferated primary vitreous.¹⁻⁴ The aetiology of the primary vitreoretinal dysplasia is genetically also heterogeneous. As regards the Mendelian mode of inheritance, autosomal recessive traits with or without systemic anomalies^{4,5} and the X-linked condition Norrie's disease^{6,7} are well documented. Chromosomal aberrations also induce typical vitreoretinal dysplasia as part of systemic syndromes. Trisomy 13 or Patau's syndrome is the commonest chromosomal disorder affecting the vitreous and retina, but other chromosomal syndromes include severe vitreoretinal dysplasia only exceptionally.⁴⁻⁸

We report the case of a girl who had the typical clinical and histopathological features of vitreoretinal dysplasia and in addition had an apparently

balanced X;10 chromosomal translocation. Neither parent had the translocation. The proposed interpretation of these data is that the translocation breakpoint involving the X chromosome disrupted the vitreoretinal dysplasia gene itself, implying that this sporadic case was indeed one of Norrie's disease due to a rare X autosome chromosomal translocation.

Case report

A Japanese female infant was born at full-term with a birth weight of 2402 g without any gestational illness or birth trauma. She appeared listless after the delivery, with absent neonatal reflexes, and had closure of the fontanelles, lack of deep tendon reflexes, and general hypotonia with intermittent twitches. The electroencephalogram showed a diffuse suppression of brain activity, though computerised tomography revealed no gross brain lesion. She had micrognathia, cleft lip, high-arched palate, and low-set earlobes, but had no visceral malformations.

Detailed ophthalmological examinations were first performed on the ninth postnatal day. There was no external anomaly, but marked malformations were found in the vitreous and retina, their degree being more severe in the left eye.

Right eye. The cornea was clear, 10×10 mm diameter. The pupil was round but reacted to light only sluggishly. The anterior chamber was clear and normal in depth. There were numerous persistent

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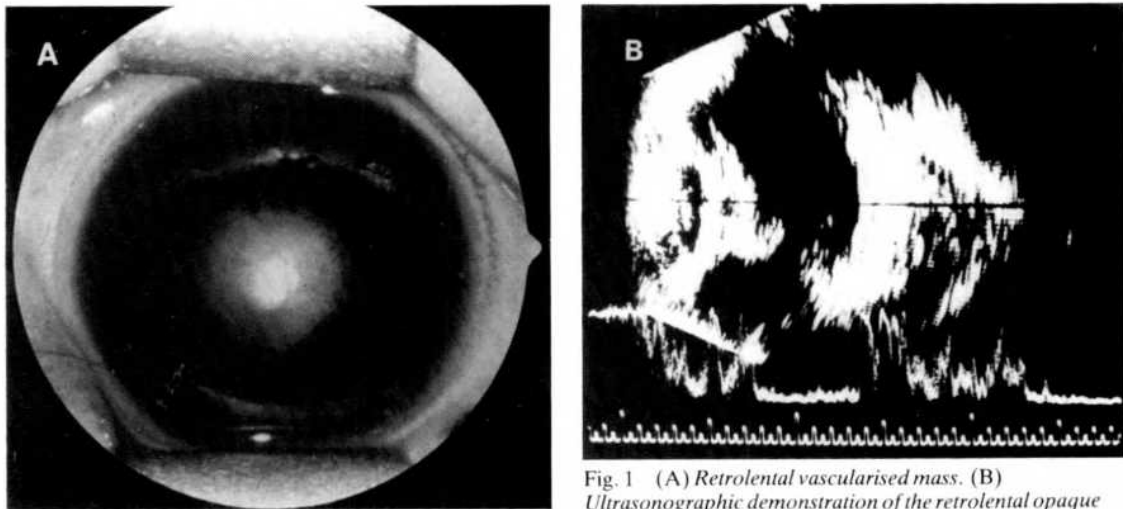


Fig. 1 (A) Retrolental vascularised mass. (B) Ultrasonographic demonstration of the retrolental opaque mass. Left eye.

pupillary membranes. The lens and vitreous were clear, making the eyeground visible. The optic disc appeared hypoplastic, with pale colour and deep cupping. The posterior eyeground was mottled with scarce, narrow retinal vessels. The macular region could not be identified. The peripheral eyeground appeared dull whitish.

Left eye. The eyeball was microphthalmic. The intraocular pressure was low in digital pressure, measuring 4 mmHg by Schiøtz tonometry. The cornea was clear, 8.5×8.0 mm in diameter. The pupil did not react to light and was dilated irregularly with mydriatics owing to posterior synechiae. The anterior chamber was shallow. The iris was partly atrophic, and numerous aberrant vessels of the iris extended radially on to the surface of the clear lens or towards the posterior chamber. Part of the ciliary processes was elongated. Just behind the clear lens a

yellowish-white vascularised mass filled the pupillary space of the anterior vitreous cavity, so that the fundus could not be visualised. Ultrasonography confirmed the microphthalmic eyeball and the presence of a retrolental opaque mass (Figs. 1A, B).

During the follow-up examinations no substantial change occurred in either eye, except that the anterior chamber of the left eye became shallower. The patient died at the age of 14 months from intractable pneumonia. The eyeballs were enucleated for medicolegal necropsy two hours after the death and examined with haematoxylin-eosin staining.

OCULAR HISTOPATHOLOGY

Right eye. This eye measured 22×20×20 mm. The cornea was entirely normal. The epithelial and stromal layers of the iris were normal, but the

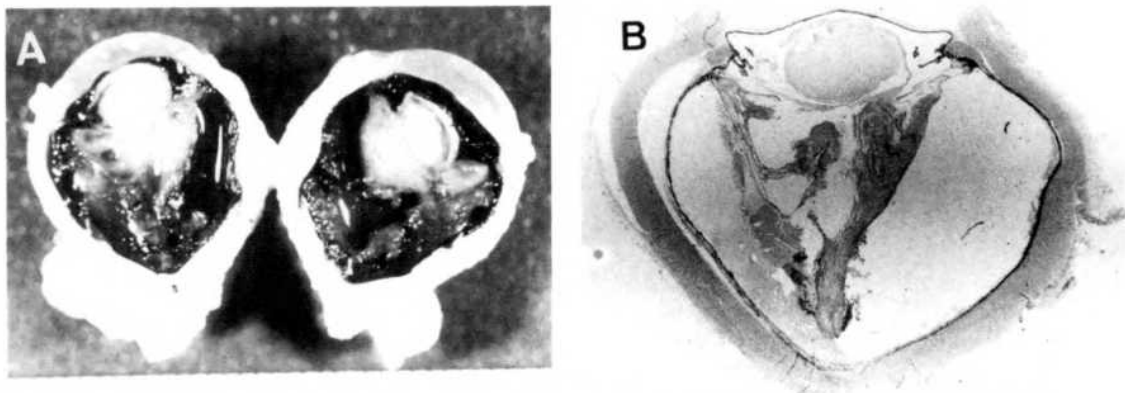


Fig. 2 (A) General appearance of the left eye. (B) Totally detached retina adherent to the retrolental fibrous tissue.



Fig. 3 Part of ciliary processes elongated. ($\times 29$).

sphincter muscle cells were not separated from the pigmented cells. The lens, ciliary body, anterior chamber angle structure were well developed. There was no aberrant tissue in the vitreous. The retina was

well developed, with the normal stratification, and there was no developmental anomaly in the neural retina or pigment epithelium, except a reduced number of retinal vessels and scarce ganglion cells with associated thin nerve fibre layer. The choroid was composed mainly of large vessels.

Left eye. This eye was evidently microphthalmic, measuring $18.5 \times 15.5 \times 15$ mm. Inspection of the sectioned eyeball disclosed a piece of detached retina attached to retrolental fibrous tissue (Figs. 2A, B). The cornea was normally developed. The iris was also normally developed, but part of its pigment epithelial layer had nodule-like proliferations. The ciliary muscles were arranged irregularly, and a part of the ciliary processes was elongated and adherent to the proliferated connective tissue behind the lens. The anterior chamber angle was immature (Fig. 3). The whole circumference of the lens had epithelial cells, and between the anterior capsule and the epithelial cell layer were present numerous aberrant cells (Fig. 4). Adherent to an irregularly curved posterior capsule of the lens was a mass of dense fibrous tissue containing numerous small vessels, which was regarded as persistent primary vitreous (Fig. 5). The bulk of the retina was completely detached from the pigment epithelium and firmly adherent to the retrolental vascularised tissue, at the periphery of which there were numerous macrophages containing melanin granules. The retina was highly dysplastic and composed of undifferentiated embryonic tissue containing a number of rosettes; the rosettes had a clear or fibrillar central lumen surrounded by fine limiting membranes and one or two layered dark nuclei; in shape they were oval, elliptical, or oblong in accordance with the plane

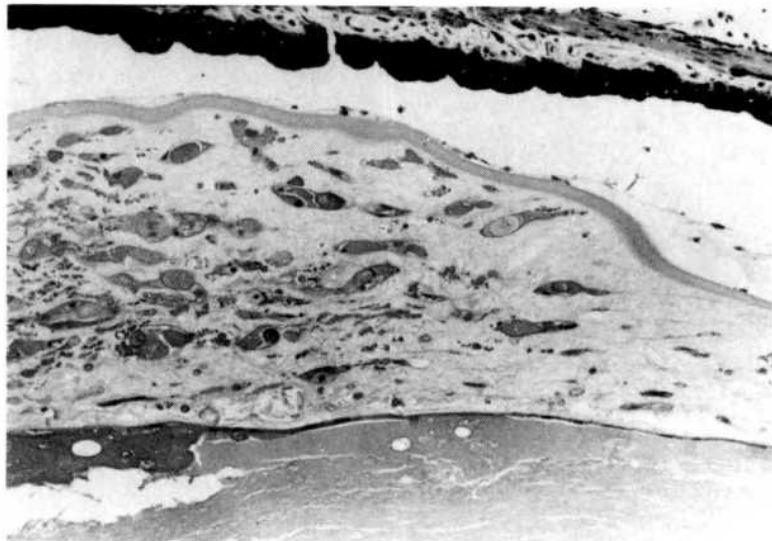


Fig. 4 Anterior part of the lens with numerous aberrant cells between the anterior capsule and epithelial cell layer. ($\times 60$).

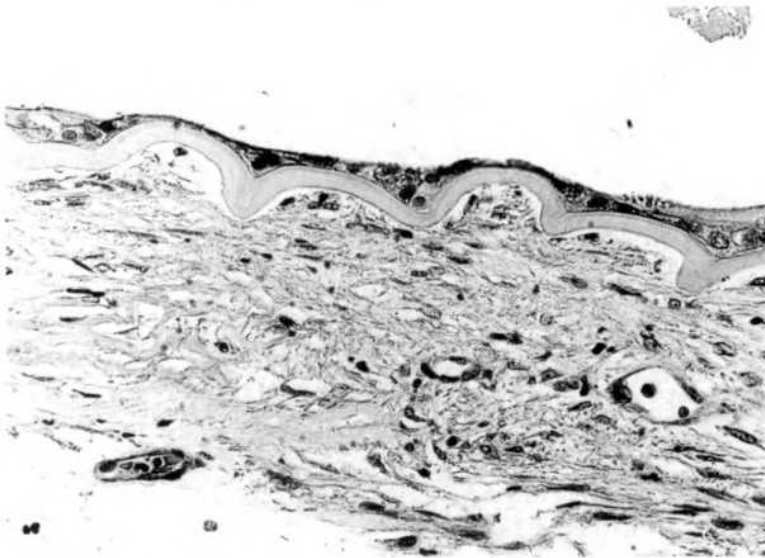


Fig. 5 Vascularised fibrous tissue adherent to the posterior surface of the lens. ($\times 60$).

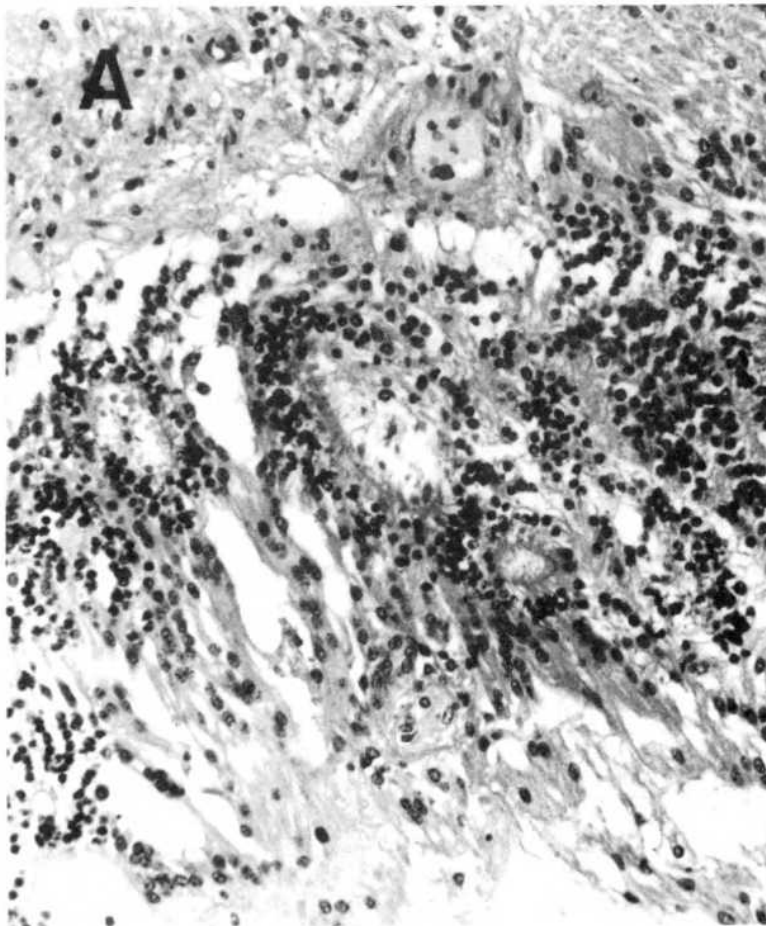


Fig. 6A Dysplastic retina with formation of rosettes. ($\times 50$).

sectioned (Fig. 6A, B). The pigment epithelium of the retina was also dysplastic, being composed of multiple layers of proliferated cells which choroidal vessels had invaded here and there. The choroid was poorly developed (Fig. 7).

FAMILY HISTORY AND KARYOTYPE ANALYSIS

The patient was the third of three children of non-consanguineous parents. The parents and siblings (a brother and sister) were examined and found to be normal, and there was no family history of systemic or ocular malformations. Chromosome analysis was performed on peripheral blood cultures and banded with Giemsa. The patient showed 46 female chromosomes with an apparently balanced reciprocal translocation between an X chromosome and a C group autosome, most probably autosome 10. The breakpoint of the X chromosome was estimated as being Xp11 (Figs. 8A, B). Thus her karyotype may be described as 46XX, t(X;10) (p11; p14), though detailed cytogenetic studies are needed to define the

breakpoint more precisely. Her parents and siblings had entirely normal karyotypes.

Discussion

The clinical and histopathological features of the patient are consistent with typical vitreoretinal dysplasia, presenting as a congenital pseudoglioma with poorly differentiated dysplastic retina, with the formation of rosettes and proliferated primary vitreous. The cause of these developmental anomalies is certainly a chromosomal aberration.

A number of chromosomal diseases have been shown to induce ocular anomalies as a part of systemic syndrome. Dysmorphic changes of the external eye together with facial malformations are the most commonly found ocular abnormalities in a variety of chromosomal aberrations. It is noticeable that a severe vitreoretinal dysplasia similar to that of the present case has been described almost exclusively in association with an excess of the genetic material of

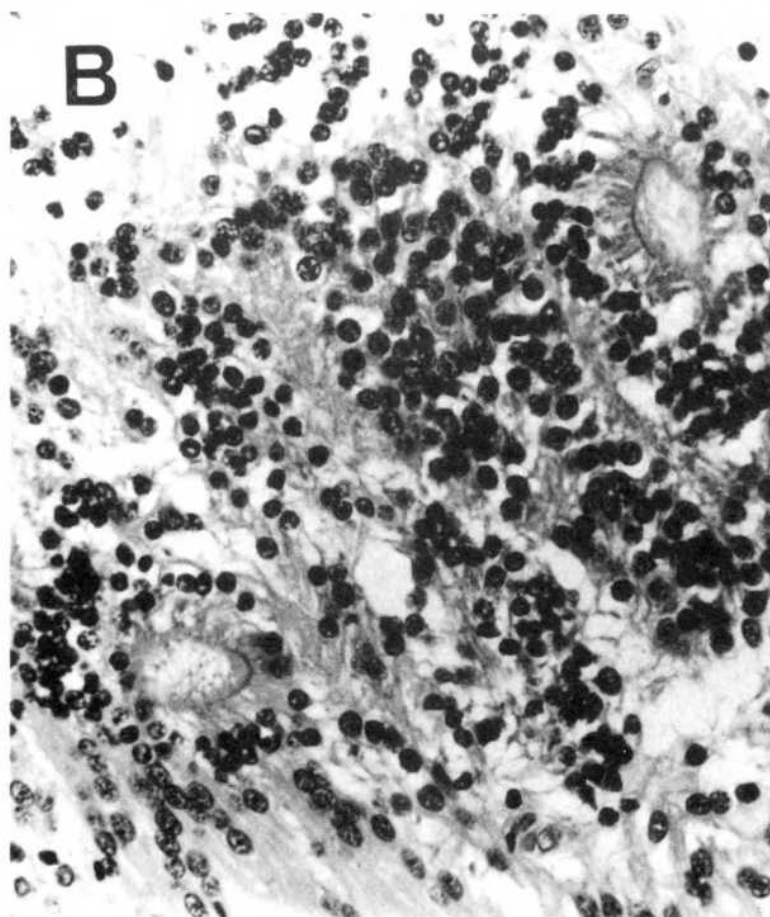


Fig. 6B Dysplastic retina with formation of rosettes. ($\times 100$).

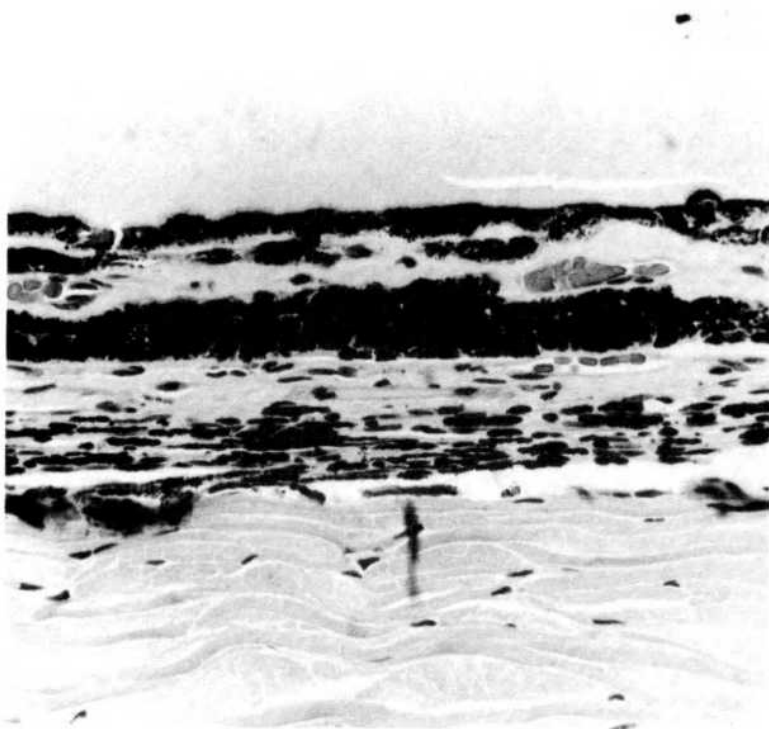


Fig. 7 Dysplastic retinal pigment epithelium and choroid, multiple layered pigment epithelium invaded by choroidal vessels. ($\times 80$).

autosome 13, its trisomy or partial trisomy, referred to as Patau's syndrome.⁸⁻¹⁰ The present case is therefore exceptional in that chromosome analysis revealed 46XX, t(X;10), a seemingly balanced reciprocal translocation between an X chromosome and one of the C group autosomes, probably autosome 10. It is most likely that this rare chromosomal aberration occurred as a *de novo* mutation in view of the normal karyotypes of the parents. Therefore Patau's syndrome can safely be ruled out, and the autosomal recessive trait of vitreoretinal dysplasia can also be excluded, since it is extremely unlikely that a new mutation at an autosome-linked gene locus and a *de novo* chromosomal translocation involving the X chromosome could occur by coincidence. Thus it is plausible that the chromosomal translocation happened to disrupt the vitreoretinal dysplasia gene itself, and the apparent translocation breakpoint Xp11 suggests the gene locus for the disease of this patient, though a precise localisation must depend on more detailed cytogenetic studies.

If the above explanation is correct, it is still necessary to explain why our patient showed the full clinical features of vitreoretinal dysplasia when she was heterozygous for the disease gene and had one normal allele. Heterozygous females of X-linked condition usually show mild, if any, clinical symp-

toms, since the X chromosome having the normal allele is inactivated in a random manner.¹¹ The reason for the full clinical picture in our patient is almost certainly that her normal X chromosome, which carries the normal allele at the vitreoretinal dysplasia gene locus, is almost inactive, either because of non-random X chromosome inactivation or because of some subsequent selection of the cells in which the mutant X chromosome is active. This non-random X inactivation in X autosome translocation has been well described.¹² In this connection it is remarkable that the degree of the clinical symptoms of the present case varied considerably between the two eyes; one eye had severe vitreoretinal dysplasia, whereas the other eye showed a relatively mild condition. This suggests a variable degree in the inactivation of the X chromosome bearing the normal allele.

A phenomenon similar to the present case has been reported in heterozygous females of X linked recessive disorders such as Hunter's disease and Duchenne muscular dystrophy. The heterozygous females of these conditions usually have normal karyotypes and no or only mild clinical symptoms. A female patient with the full clinical picture of Hunter's disease showed a *de novo* balanced reciprocal chromosomal translocation 46XX, t(X;5) with the

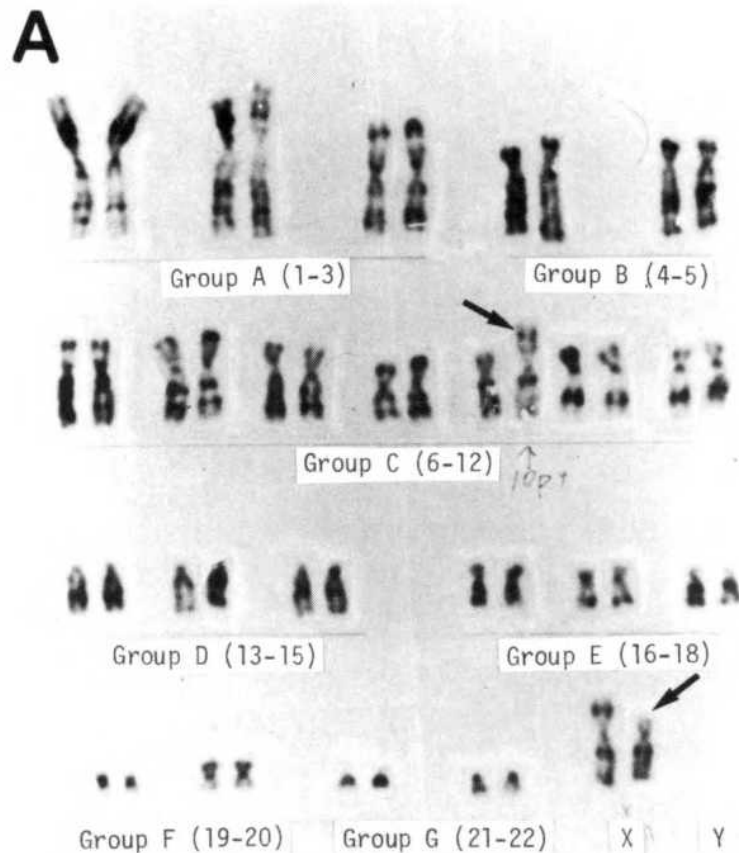


Fig. 8A Giemsa-banded karyotype of the patient.

X chromosome translocation breakpoint being between Xq26–27.¹³ More than five unrelated female patients with the typical clinical features of Duchenne muscular dystrophy were reported to have an apparently balanced reciprocal X autosome translocation 46XX, t(X;A), and, although different autosomes were affected among the patients, the breakpoint on the X chromosome was invariably Xp21.¹⁴

It is tempting to assume with reference to the above reports that the present case was indeed one of Norrie's disease, a rare X-linked recessive disorder characterised by bilateral blindness due to severe vitreoretinal dysplasia and in some instances by associated mental retardation and hearing impairment. Heterozygous females do not show any clinical symptoms with normal karyotypes.^{6,7} The clinical and histopathological features of the present case are consistent with the full clinical symptoms of Norrie's

disease except for the associated facial dysmorphic anomalies, which are not usually found in this disease.^{6,7} By analogy with the sporadic female patients of X-linked disorders mentioned above, it may be possible to conclude that the present case had Norrie's disease due to X autosome translocation. If this interpretation is correct, it is suggested that the gene locus of Norrie's disease is located at the short arm of the X chromosome.

Genetic linkage studies have suggested a loose linkage of Norrie's disease with the glucose-6-phosphate dehydrogenase locus,⁶ and no measurable linkage with Xg blood group locus.^{6,15} The former locus has been assigned to the long arm of the X chromosome, Xq28, and the latter to the short arm of the X chromosome, Xp2.¹⁶ Our assumption for the Norrie's disease gene locus, the short arm of the X chromosome, seems inconsistent with these genetic linkage data. In any event family studies of Norrie's

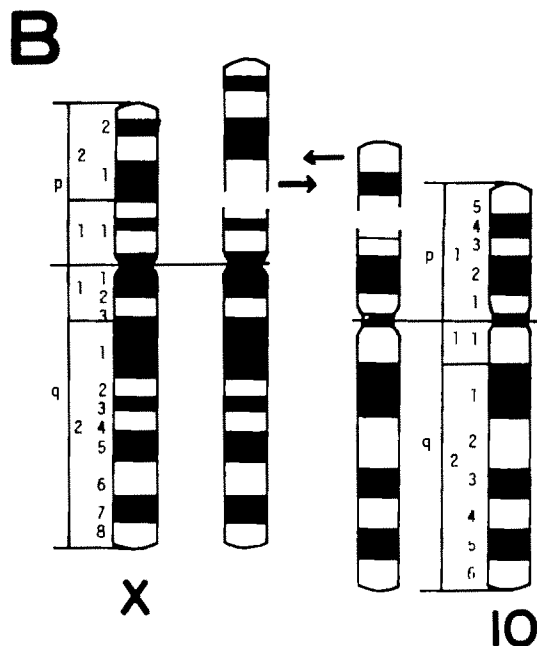


Fig. 8B Idiogram showing the apparently balanced reciprocal translocation between chromosome X and 10 (arrows).

disease with reference to the linkage with various gene loci mapped on the X chromosome, and detailed chromosome analysis on sporadic female patients with features of Norrie's disease, will be required for a more precise localisation of the Norrie's disease gene.

This study was supported in part by a research grant for retino-choroidal atrophy from the Japanese Ministry of Health and Welfare.

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Cryptophthalmos: a report on three sibling cases

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SUMMARY Three siblings, two females and one male, with the rare disease, cryptophthalmos, are reported on. Cryptophthalmos is usually familial, inherited as an autosomal recessive trait. The clinical manifestations indicate that the eyeball is present but disorganised; the lid muscles, extraocular muscles, and the nerve elements controlling ocular movements in the brain are developed. Treatment is of no avail, but in unilateral cases the partial lid coloboma, anterior symblepharon, and corneal opacification of the opposite eye may be somewhat improved by surgery.

Cryptophthalmos is a rare congenital anomaly characterised by an uninterrupted continuity of the skin of the forehead with that of the cheek, resulting in total ablepharon. It was first reported in 1872 by Zehender and Manz,¹ and only two cases have been presented in China.^{2,3} A family is now reported here in which three of the five siblings were affected (Fig. 1, 2).

Case report

Case 1 (III₁) was the first child of the family, born at term in 1949, and was seen on 30 May 1982 for bilateral congenital absence of palpebrae. During pregnancy her mother, except for malnutrition, had no history of noticeable illness, trauma, or exposure to toxic agents or radiation. At the age of 3 months the baby was admitted to hospital and the skin overlying her orbits incised, but no corneas were found.

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At 33 years old the patient looked pale, was fat, was 128 cm in height, and had normal neuropsychological development and average intellect (Fig. 3). The upper and lower limbs measured 57 cm and 67 cm in length respectively. Both legs were bowed leftwards. An unusual growth of hairs extending from the temples forwards and downwards to both sides of the forehead made the haired areas appear triangular in shape. The eyebrows were almost absent; only a few remnants were visible near the root of the nose.

On the skin covering the orbit there was a horizontal shallow groove, 3 by 0.2 cm. A domed prominence about the size of a pea in the centre of the orbit indicated the undeveloped eyeball. A sudden sound elicited a reflex wrinkling of the orbital skin, but exposure to strong light failed to evoke a similar response. Voluntary and conjugate movements of both occult globes could be perceived. No lashes or lid structures, including tarsi, were found. The karyotype showed nothing remarkable.

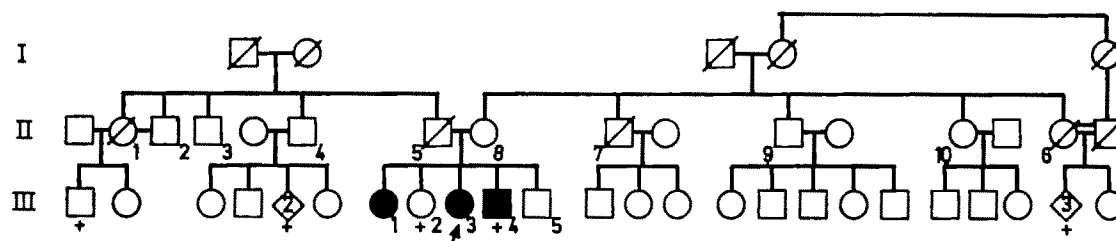


Fig. 1 Pedigree of the proband (arrow) and his family. III₁₋₅: full-term delivery. III₁: born in 1952, died at 5 months. III₂: born in 1956. II₅: 58 years old, died at 1982. II₈: 49 years old



Fig. 2 From left to right: II₈, III₁, and III₃.

Case 2 (III₃) was born with right cryptophthalmos in 1953. Poor vision of the left eye necessitated optical iridectomy five years ago (Fig. 4). On physical examination the pattern of hair growth and the appearance of the right side of the face were similar

to those of case 1. In the left eye she had: vision 0.06; coloboma of the medial two-thirds of the upper lid (Fig. 5), which had no lashes and was adherent to the cornea, which showed scattered opacifications; an anterior chamber slightly deeper than normal; the



Fig. 3 III₁, bilateral cryptophthalmos.



Fig. 4 III₃, right cryptophthalmos.



Fig. 5 Left eye of III₃, showing coloboma of medial two-thirds of the upper lid, which is adherent to the cornea.

outer part of the brownish iris lacking; the pupil large and reactive; the lens clear; the fundus invisible; the intraocular pressure normal on palpation. The karyotype was normal.

Case 3 (III₄) was born in 1954 with a facial appearance identical with that of case 1. He lived only 2 months.

No other family members were affected. Their parents were not consanguinous and had no congenital abnormalities. The father died of cerebral haemorrhage during the final follow-up of the family in 1982. Palm and finger prints and the karyotypes of III_{1,3,5} and II_{5,8} showed nothing abnormal.

Discussion

These three cases have the typical symptoms of cryptophthalmos, some of which indicate certain histogenetic facts. Blink-like movements indicate the presence of the lid muscles. Absence of response to

strong light denotes a disorganised globe without vision. Voluntary and conjugate eye movements indicate that the extraocular muscles and the nerve elements controlling ocular movements in the brain stem and cerebrum have developed.

Van Duyse in 1889 found that the parents of cryptophthalmos patients were related,⁴ and it is now believed to be a hereditary disease. In this pedigree the normal karyotypes of the four family members tested, including two sufferers from the disease, rule out chromosome aberration and indicate gene mutation. The family history suggests autosomal recessive transmission of the trait, as has usually been reported.

Because the eye is disorganised and the conjunctival sac is usually absent, recovery of sight and reconstruction of the lid and conjunctival sac by plastic surgery are impossible.^{2,5} In a unilateral case, with malformations of the opposite eye such as partial lid coloboma, anterior symblepharon, and cornea opacifications, the vision and facial appearance can be improved only partially by operation, because developmental abnormalities, especially of the posterior segment, are almost always present to certain degree, rendering complete recovery impossible.

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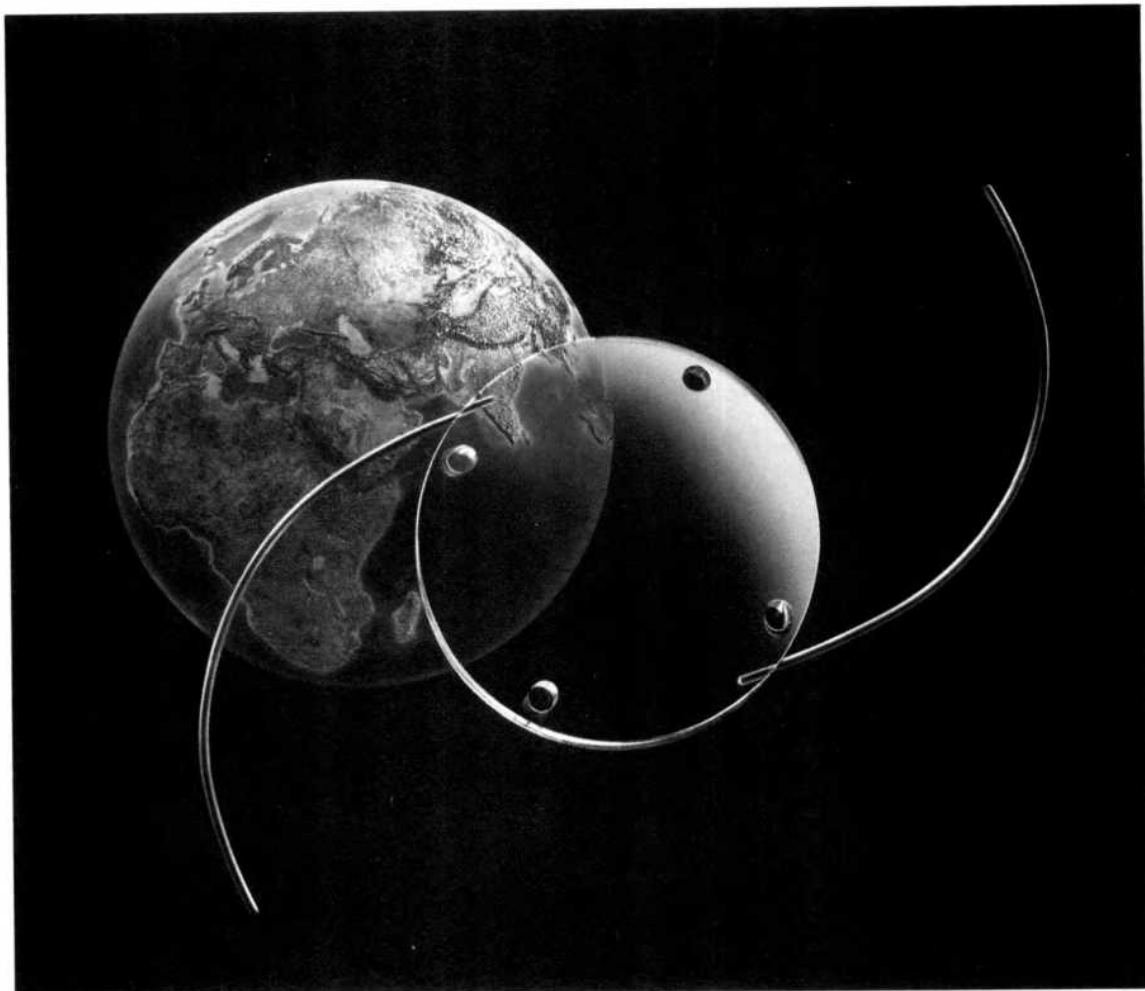
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Sheep tick in the eyelid

B K McLEOD

From the West of England Eye Infirmary, Exeter.

SUMMARY The uncomplicated removal of a tick, *Ixodes ricinus*, from the lid is described. Methods of removal of ticks, their natural history, and potential complications are discussed.

An 11-month-old girl presented to the Casualty Department of the hospital after being irritable during the previous night; she was found to have a swelling of the left lower lid the next morning. She lived on a farm with her parents and had been previously healthy, with normal development.

Examination revealed erythema of the left lower lid, at the centre of which was a dark raised lesion. The preauricular lymph nodes were not enlarged and the globe itself was normal, with no conjunctival injection. Closer examination of the lesion showed it to be the body of a tick, which was pulsating, and the head parts were buried in the skin of the lid (Fig. 1). The patient was wrapped in a blanket, the eye was anaesthetised with Ophthaine (proxymetacaine Hll with chlorbutol, benzalkonium chloride, and glycerol), and a chalazion clamp was placed over the body of the tick. A drop of isopropyl alcohol was applied to the body of the tick and the clamp slowly tightened. The tick was gradually extruded and no

obvious mouth parts were seen embedded in the skin (Fig. 2).

The patient made an uneventful recovery, the erythema subsided, and the skin lesion healed quickly.

The tick was later identified as a sheep tick of the species *Ixodes ricinus* (Fig. 3).

Discussion

A few cases of ticks in the eyelid have been reported^{1,2} and one case of a tick attached to the conjunctiva, which was removed with further problems.³

Ticks are blood-sucking arthropods of the family Ixodidae. The genus *Ixodes* has at least 16 species, of which *Ixodes ricinus* is the commonest in this country.⁴ Found especially in Scotland, Wales, and the West Country, it is a moderately large brown-black tick, its colour varying with its degree of engorgement with blood. Like other ticks it is made up of a body, a capitulum, and palpi or mouth parts. *Ixodes ricinus* is a three-host tick, and all stages of development may exist on the same host. The adult tick waits for a passing host on the tips of grasses, and, on its obtaining a host, the penetrant mouth parts easily pierce the skin assisted by salivary secretions which act as an anchor. Blood is required to aid reproductive and metabolic functions, and

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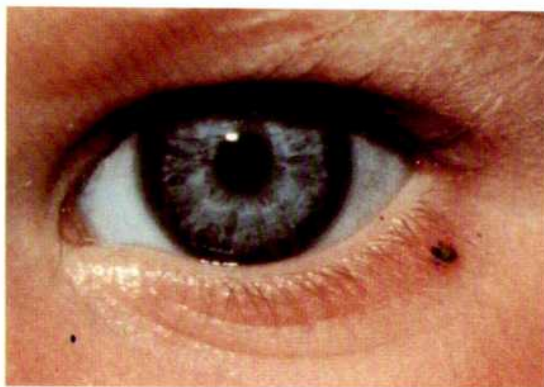


Fig. 1 Patient with tick embedded in left lower eyelid.

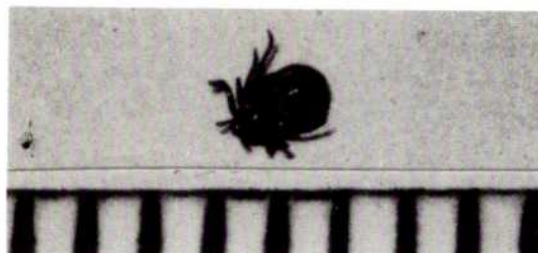


Fig. 2 Tick removed intact. (Millimetre scale).



Fig. 3 Tick mounted on a 21G needle.

females feed on the host for seven to 13 days, then drop to the ground and lay several thousand eggs. Larvae feed for three to five days before moulting to the nymph form, which in turn imbibes host tissue and eventually becomes an adult. The most common hosts in this country are cows, sheep, and dogs.⁵ This patient had been in close proximity with the dogs on her parents' farm, which had been known to carry ticks in the past, and they were thought to be the most likely source of infection in this case.

An inflammatory reaction usually follows the attachment of the tick to its host. Saliva introduced by the palpi generates chemotactic factors which result in the influx of neutrophils. Host tissue destruction is aided by the neutrophil derived elastase and collagenase.⁶

Tick bites may facilitate the entry of a secondary infection, with formation of an abscess. Even in the absence of infection a bite can itself produce symptoms of malaise,⁷ and delayed reaction has been

reported which results in a granuloma progressing from days to months even though removal was considered complete.⁸ Incomplete removal results in the mouth parts left in the skin forming a tick nodule that may be confused with an epidermal cyst or naevus.⁹

Ixodes ricinus is the vector of the causal organisms responsible for livestock diseases such as louping ill, tick-borne fever, Redwater fever, and piroplasmiasis but has not been implicated in the spread of disease in this country.⁴ In North America the dog tick is a known vector of *Francisella tularensis*, the causative organism of tularaemia and *Rickettsia rickettsii*, the organism causing Rocky Mountain spotted fever, is also tick-borne.

Many techniques have been described for the removal intact of embedded ticks, including the use of sprays and the application of ether and iodine. Deodorised kerosene and camphorated phenol caused the voluntary detachment of 25% of treated Lone Star ticks.¹⁰ When the tick is embedded close to the eyelid margin, these techniques are not applicable and mechanical removal is recommended. A drop of isopropyl alcohol carefully applied stopped the tick pulsating and helped loosen its grip in this case.

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Obituary

K. Rubinstein, MD, FRCSEd, DOMS

Kazimierz Rubinstein, formerly consultant ophthalmic surgeon at the Birmingham and Midland Eye Hospital, died suddenly on 25 June 1985 aged 69 years. He was born and educated in Lodz, Poland, and started his medical studies in Wilno. These were interrupted by the Russian occupation of East Poland at the beginning of the second world war, but with incredible boldness and enterprise he managed to leave in order to join the Polish Forces in the Middle East. There he was given the chance to complete his medical training at the University of Beirut. Afterwards he rejoined the Polish Forces as medical officer attached to an artillery unit in Italy. He was well liked by the 'gunners,' and his courage in the field was rewarded by a Polish Military Cross.

After demobilisation he started his ophthalmic specialisation in Sheffield, and having passed the DOMS and FRCS examinations he obtained a consultant post in Burton-on-Trent. He was enthusiastic in his work and had a passion for anything new and challenging. Having a large number of patients with squint, he devoted special interest to the surgery of the oblique ocular muscles, obtained considerable experience in this subject, and published his results. A few years later he was appointed a consultant in Birmingham.

The new technique of cryosurgery appealed to him, and with the help of a low-temperature engineer he constructed a cryosurgical unit based on liquid nitrogen. He also became fascinated by fluorescein fundus angiography, and, mastering this technique, he used it combined with the application of laser in the treatment of diabetic retinopathy and senile retinal dystrophy. Publishing his results, he gained international recognition.

Ruby was very helpful to his fellow colleagues and inspired many with his enthusiastic approach to ophthalmology. For his friends Kazik's sense of humour was a most endearing feature and made him a perfect companion. His favourite sport was skiing in the Alps; later on he changed it to water skiing on the Mediterranean. It is tragic that soon after his retirement four years ago his health deteriorated and so he could not enjoy a golden autumn of his life with his wife Eileen and his sons Matthew and Stephen. JLR

Book reviews

Computerized Visual Fields: What they are and how to use them. Eds. WILLIAM R WHALEN AND GEORGE L SPAETH. Pp. 414. US\$75.00. Slack: New Jersey. 1985.

Von Graefe in 1856 is credited with realising the clinical importance of detecting visual field loss. Aubert in 1857 designed the first arc perimeter, consisting of two semi-circular curved metal rods so that the patient when looking with one eye at the centre could see an object being moved in his peripheral field. Bjerrum in 1890 emphasised the importance of the central field and designed a flat black

screen on which to chart central field defects. This method remained pre-eminent in glaucoma work until the 1950s, when the bowl perimeter with standard background illumination and testing under photopic conditions was introduced. Goldmann noted the relationship between stimulus size and luminance and paved the way for establishing reproducible perimetric testing so essential for the management of chronic ocular disease, notably glaucoma. Widespread adoption of bowl perimetry was rapidly followed by the training of perimetrists, on whom busy ophthalmologists were increasing to rely. The nature of visual field testing allowed innovators such as Dubois-Poulsen and Majas and Fankhauser and Parcel in the 1960s to investigate automatic automated perimetry. Standardisation of test conditions and the advent of the microchip allowed the development of the partially and then the fully automated perimeter.

Recognition of the advantages of the automatic perimeter with freedom from perimetrist shortages and the production of numerical print-outs has generated worldwide interest. In view of that interest Whalen and Spaeth have written, in conjunction with fourteen others, a manual on automatic perimetry. Based on their experiences with the standard bearer of automatic perimetry, the book contains lucid chapters describing programs, reproducibility, normal values, and the results seen in glaucoma and other disorders of the visual system. The information given here leaves the reader in no doubt that this type of perimetry is the greatest advance after the Goldmann bowl perimeter. And yet a word of caution.

Caution must be exercised on two fronts. Firstly, as Armaly noted in the final chapter, numbers (as the print-outs are recorded) alone should not mislead one into a notion of added accuracy or reliability. With threshold perimetry the ophthalmologist becomes acutely aware of the variability of the human response. Secondly, many patients need to be trained in responding to the automatic perimeter. Many are scared of being controlled by a machine and cannot give of their best. Results are worthwhile only after the patient has been tested twice or on even more occasions. The less intelligent the patient, the less reliable the results. For the anxious or stupid the automatic perimeter is no substitute for the calm voice of the perimetrist, who, metaphorically holding the patient's hand during the test, is more likely to lead him on to give of his best.

Automatic perimetry is a microchip miracle exploring new undulations on the slopes of Traquair's island of vision. It is of value for those patients who can respond; for the rest we shall still need to remain on manual.

ROGER A HITCHINGS

External Infections of the Eye: Bacterial, Viral, Mycotic with Noninfectious and Immunologic Diseases. 3rd Edn. By HELENA B FEDUKOWICZ AND SUSAN STENSON. Pp. 369. £71.95. Appleton-Century Crofts: Norwalk, Connecticut. 1985.

This is a well written, easily read, comprehensive survey on the subject of external infections of the eye. It deals fully with the different bacteria and viruses that cause such

infections and gives an excellent account of their identification, with very useful colour plates to illustrate the characteristics of each organism itself. It would have helped, though, if there had been tables summarising the characteristics of different bacteria, so that, for instance, the reader could readily determine which organisms were Gram-positive and which Gram-negative.

It suffers from being orientated towards the causes of the infections, so that the clinical signs, symptoms, and management are in a secondary place. This gives a lopsided approach to the book and makes it difficult for the reader to determine the relevant diagnosis and treatment. For example, in the diagnosis of staphylococcal infection of the lids no mention is made of the differential diagnosis of squamous blepharitis and what it may be associated with, and in the description of herpes simplex stromal disease no mention is made of other causes, apart from herpes simplex, of disciform keratitis.

In discussing herpes zoster ophthalmicus the authors point out that, once steroids have been started, meticulous tapering may be necessary to avoid recurrences, but they do not mention the length of the period over which this tapering has to be done. In fact it needs to be done over at least a year to prevent a rebound recurrence. In the section on measles keratitis emphasis should have been made on how this severe keratitis is a disease of poor hygiene or debilitation, and as such is a frequent cause of blindness in deprived countries in the tropics.

There are omissions. In the treatment of seborrhoeic blepharitis no mention is made of the use of tetracycline, where it has such good effects. In the herpes zoster section no mention is made of late corneal epithelial involvement with mucoid plaques, which are often found in anaesthetic corneae, nor is there any mention of their treatment. Rather, the authors say, 'changes may vary from the mildly dry eye state to severe lid deformities and corneal thinning.'

In the assessment of yet another text book the question has to be asked whether this particular one fills a gap in our already crowded shelves. The conclusion is that it does, and so it is recommended.

JAMES I MCGILL

Laser Therapy of the Anterior Segment: A Practical Approach. By LOUIS SCHWARTZ, GEORGE SPAETH, GARY BROWN. Pp. 153. £47.35. Slack: New Jersey. 1984.

This is a most useful practical book covering all aspects of laser therapy of the anterior segment with the use of both continuous wave and short pulse lasers. The text is clear, well illustrated with numerous illustrations, and includes many useful references. There are chapters on gonioscopic evaluation of the anterior segment, argon and YAG iridotomy, laser trabeculoplasty, other argon applications, YAG laser capsulotomy, and division of vitreous in the anterior segment.

Minor criticisms include a somewhat didactic approach in some sections, the fact that surgeons rarely treat 360° in one session now, no mention of the Ritch lens, and patients with narrow angles prior to laser trabeculoplasty are more likely to undergo a peripheral iridotomy or peripheral iridectomy than iridoplasty. YAG laser therapy has advanced since these chapters were written. There is no mention of corneal

endothelial damage. The capsulotomy energy levels today would be regarded as being too high, and the statement that 'further retraction of the capsule after the time of capsulotomy is unusual' is not most surgeons' experience.

However, this is a most useful book and fulfils its aims to familiarise the ophthalmologist with the major uses of laser in the anterior segment.

J D JAGGER

The Ocular Lens: Structure, Function, and Pathology. Edited by HARRY MAISEL. Pp. 479. \$102.00. Marcel Dekker: New York. 1985.

This book gives an overall view of lens anatomy, genetics, physiology, biochemistry, and biophysics as each is successively related to the crystalline lens. Towards the end of the book special attention is given to lens structure and biochemistry with regard to the problems of cataract, while the final chapter considers the impact of lens research on patient care.

The book thus has something for everyone interested in the crystalline lens. The bibliography following each chapter is therefore, at times, somewhat limited. Nevertheless, for those wishing to get an overall picture of lens research and its implications for clinical practice at the present time, it can be highly recommended.

R F FISHER

Rob and Smith's Operative Surgery. 4th edn. **Ophthalmic Surgery.** Eds. THOMAS A RICE, RONALD G MICHELS, WALTER J STARK. Pp. 445. £65.00. Butterworths: Sevenoaks, Kent. 1984.

This is the ophthalmology volume of the 4th edition of *Rob and Smith's Operative Surgery*, the large series that covers the entire field of operative surgery. Although both the original and the current editors of the series are British, the contributors to this volume are almost all eminent American ophthalmologists, largely from the Wilmer Institute, each contributing a chapter or two in his own field of expertise. The editors are to be congratulated on exerting sufficiently strong an influence to make the book a coherent whole rather than a series of separate units. The chapters are all of a similarly high standard, with a clear and easily read text and excellent diagrams (with a few photographs) in black and white, which probably convey information more precisely than operative photographs. The references are full and generally appropriate (though some British authors may feel a little neglected) and the inevitable absence of the most recent information is probably beneficial. This is a book describing standard established modern ophthalmic surgery rather than developing techniques, and there is thus little to be found of procedures still under evaluation such as radial keratotomy and implants for glaucoma drainage surgery.

It is the reviewer's experience that previous editions of this book have not been widely read in Britain, and the reasons for this are not clear. This present edition is first class in every way. It can be highly recommended as a standard reference book that should be readily available to both training and trained ophthalmologists. Even to the former its moderate size should not be daunting.

M G FALCON

The Nd-YAG Laser in Ophthalmology: Principles and Clinical Applications of Photodisruption. By ROGER F STEINERT AND CARMEN A PULIAFITO. Pp. 154. £48.50. Saunders: Philadelphia. 1985.

This is an excellent book by two well known authors, and is to be recommended for those who wish to acquire an understanding of the neodymium-YAG laser and its clinical application. It is divided into two sections, the first covering laser fundamentals, optical breakdown, photodisruption, laser tissue interaction and the eye, and instrumentation. The second part discusses the clinical applications for both the anterior and posterior segments. The chapters on capsulotomy, pupillary membranes, and intraocular lenses are excellent. However, it is a shame that there is not equal coverage of iris procedures, especially as for most ophthalmologists capsulotomy and iridotomy are the commonest indications for YAG therapy. This may be because iridotomy in the USA is still investigational. A further criticism is that there is no mention of corneal endothelial damage, seen especially with increasing number of pulses and higher energy levels.

This is a clear well laid out book that makes essential reading for those embarking on the rapidly expanding field of YAG laser microsurgery.

J D JAGGER

Recent Advances in Ophthalmology. Vol. 7. Eds. S I DAVIDSON AND F T FRAUNFELDER. Pp. 223. £22.00. Churchill Livingstone: Edinburgh. 1985.

This latest *Recent Advances in Ophthalmology* contains very well selected topics which are currently the subject of research and discussion in ophthalmology. Seventeen authors from the UK and the USA (with one exception, Professor Eisner, of Berne, Switzerland) cover therapy of herpes simplex, anterior chamber surgery, viscoelastic substances, radial keratotomy, intraocular lenses, congenital cataract, ocular phototoxicity, vitreous surgery, diabetic retinopathy, malignant melanomas, macular disease, glaucoma, and laser trabeculoplasty.

The illustrations are entirely black-and-white but of a high quality and well laid out with clear print. Each section usually provides a short introduction providing interesting background leading to the present advance in the subject. It is always satisfactory to be reminded that most advances in science are by gradual evolution. This evolutionary aspect is discussed in the section on intraocular lenses, but it is disappointing that this section has so little detail on complications, which are listed rather than given evaluation. Anterior segment surgery includes refractive keratoplasty and corneoscleral grafting, which has received wide attention in the ophthalmic literature. Pterygium surgical techniques are also included, but the equally important post-operative management, especially with topical steroids, gets no mention.

The selection of topics has been very good, and all practising ophthalmologists will find much to interest them. Of necessity there are a fair number of open ends in the topics discussed, but this adds to the value of the book and provides ideas for future advances. The references at the end of each section are full and again may lead the reader to further literature search.

JAMES L KENNERLEY BANKS

Ocular Differential Diagnosis. 3rd Edn. By FREDERICK HAMPTON ROY. Pp. 466. US\$30.00. Lea and Febiger: Philadelphia. 1984.

This book consists of lists of differential diagnosis set out in order of tissues or function involved, together with a short section of general signs and symptoms. There is an initial list of section headings, and each section begins with a list of subjects. While most lists are compiled with headings only, there are occasional remarks and even more rarely tables to assist in differential diagnosis. Each list is followed by references to the relevant ophthalmic literature.

Clearly this is a reference book to consult in times of difficulty. The text will appeal strongly to some readers, but others will find the unevenness of treatment and apparently capricious compilation of the lists irritating. The American terminology is also at times confusing. Much of the information can be obtained from standard works of reference, but some of the lists concerning symptoms or signs which cut across the systematic consideration of disease are very valuable.

This is not a book for the beginner, but an aide mémoire for the practising ophthalmologist, though having identified the possible diagnoses he will need in most cases to consult other sources for information about their differentiation. One of the most useful features is the full listing of drugs capable of producing each particular symptom or sign as a toxic effect. Certainly opinions will differ about the inclusions in and omissions from the lists. But then all lists of diagnoses are to some extent artificial and their bounds a question of semantics.

Perhaps the best understanding of the work, which is clearly the result of immense labour, is found in the author's preface, 'Material for this book has been used in computer systems to assist the ophthalmologist.'

D W HILL

Computer Essentials for the Ophthalmologist. Eds. DONALD R. SANDERS and GERALD E MELTZER. Pp. 143. US\$24.50. Slack: New Jersey. 1984.

This slim book with plastic bindings has as its objective the introduction of the ophthalmologist to computer technology. It contains chapters on the history of computers and how they work. Advice is given on the choice and purchase of the type of machine that might be of use to the ophthalmologist in a professional rather than a domestic capacity. The facilities offered by such common application packages as word processing, database, and spreadsheets are fully described.

This is a useful book and a reasonable start for any ophthalmologist seeking to become better acquainted with computers.

D J POWELL

Contemporary Issues in Ophthalmology. Vol 1. **Herpes Simplex Infections of the Eye.** Edited by FREDERICK C BLODI. Pp. 171. £37.00. Churchill Livingstone: Edinburgh. 1984.

This short volume has chapters by several authors covering some important topics on herpes simplex infections of the eye. The first and last chapters are particularly useful, giving

concise and contemporary analysis of the eye disease and management. My only criticism is that I would have expected more basic science as far as the virus itself was concerned and the antiviral agents used. Apart from this I found the book very readable, interesting, and informative. Priced at £37, it is within the grasp of most ophthalmologists.

RONALD J MARSH

Atlas der Kontaktlinseanpassung. By WULF EHRICH. Pp. 169. DM.178.00. Ferdinand Enke Verlag: Stuttgart. 1985.

In a manual devoted to teaching the art of contact lens fitting every picture is worth a dozen lines of writing. This beautifully produced atlas contains 497 excellent photographs to compliment the short and incisive text, making this a highly recommendable addition to the ophthalmologist's library. Indeed one would hope that it also became compulsory reading for all contact lens practitioners in training. The theory and practice of contact lens fitting are illustrated step by step, and at times a picture is repeated in

order to emphasize a point of technique. The text has been kept to a minimum, yet it is comprehensive and didactic.

It is hard to find any fault with this useful book, and an English translation would prove very popular.

T J FFYTCH

Moderne Augenrefraktometer. Bucherei des Augenarztes. Vol. 102. By BERNHARD RASSOW AND WOLFGANG WESEMANN. Pp. 86. DM.32.00. Enke: Stuttgart. 1984.

The 102nd volume of the on-going series 'Bucherei des Augenarztes' is devoted to an evaluation of refractometers, with special attention being paid to an automatic infrared machine. The mathematical and optical principles of refractometers are discussed fully together with the results of tests on model eyes. The text is very technical and likely to have only a limited appeal to clinical ophthalmologists.

In this long series of textbooks, many of which can be enthusiastically recommended, volume 102 will not feature highly in the popularity stakes.

T J FFYTCH

Notes

Herpetic eye diseases

The International Conference on Herpetic Eye Diseases will be held at Lake Tahoe, California on 6-8 September 1986. The topics include experimental and clinical studies of eye infections with herpes simplex virus, varicella zoster virus, cytomegalovirus, and E-B virus in the areas of virology, pathogenesis, latency, immunity, antiviral chemotherapy, interferon, and clinical management. Deadline for abstracts is 5 April 1986. Further information from C R Dawson or J O Oh, Francis I Proctor Foundation, Room S-315, University of California, San Francisco, California 94143, USA.

Cataract congress

The Welsh cataract congress will be held on 11-13 September 1986 at the Cullen Eye Institute, Baylor College of Medicine, Houston, Texas. Further details from Eula Mae Chikis, Cullen Eye Institute, Baylor College of Medicine, 1 Baylor Plaza, Houston, Texas 77030, USA.

Sixth International Orthoptic Congress

The sixth International Orthoptic Congress will be held at the Harrogate Conference Centre, Harrogate, England on 29 June to 2 July 1987. Further information from the Secretary, British Orthoptic Society, Tavistock House North, Tavistock Square, London WC1H 9HX.

Ophthalmic prize

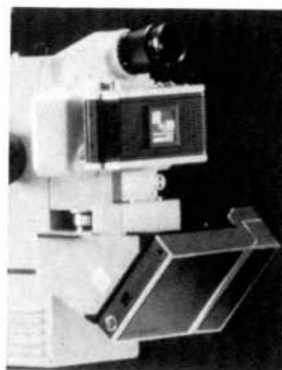
The third Ludwig von Sallman prize will be awarded at the 7th International Congress of Eye Research to be held on 25 September-1 October 1986 at the Nagoya Kanko Hotel, Nagoya, Japan. This award is for an outstanding achievement in ophthalmology and vision. The recipient will be determined by a committee composed of Dr Christina Enroth-Cugell, Dr Edward Norton, Dr Peter Gouras, and Dr Henry Wagner. Further information and nomination forms obtainable from: Peter Gouras, MD, Chairman of the von Sallmann Prize Committee, Columbia University, Box 18, 630 West 168 Street, New York, New York 10032, USA.



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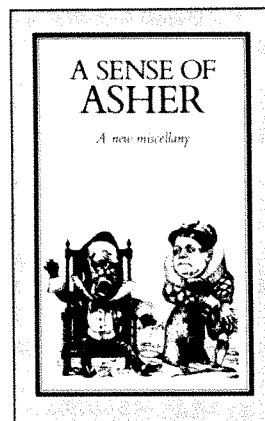
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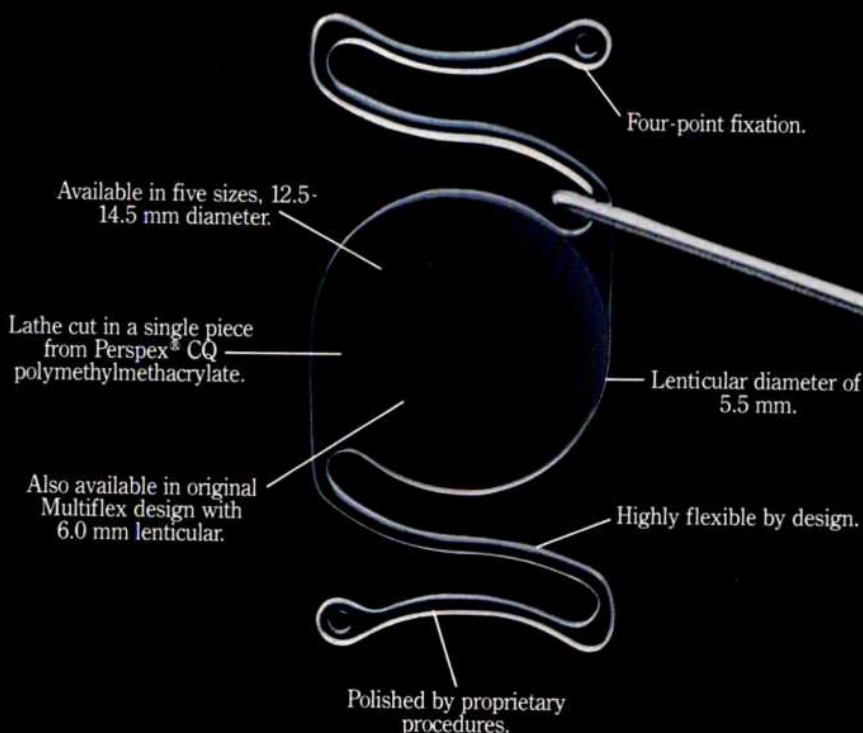
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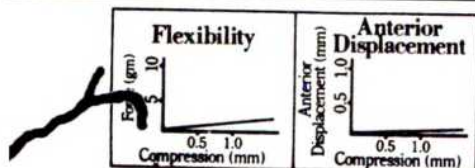
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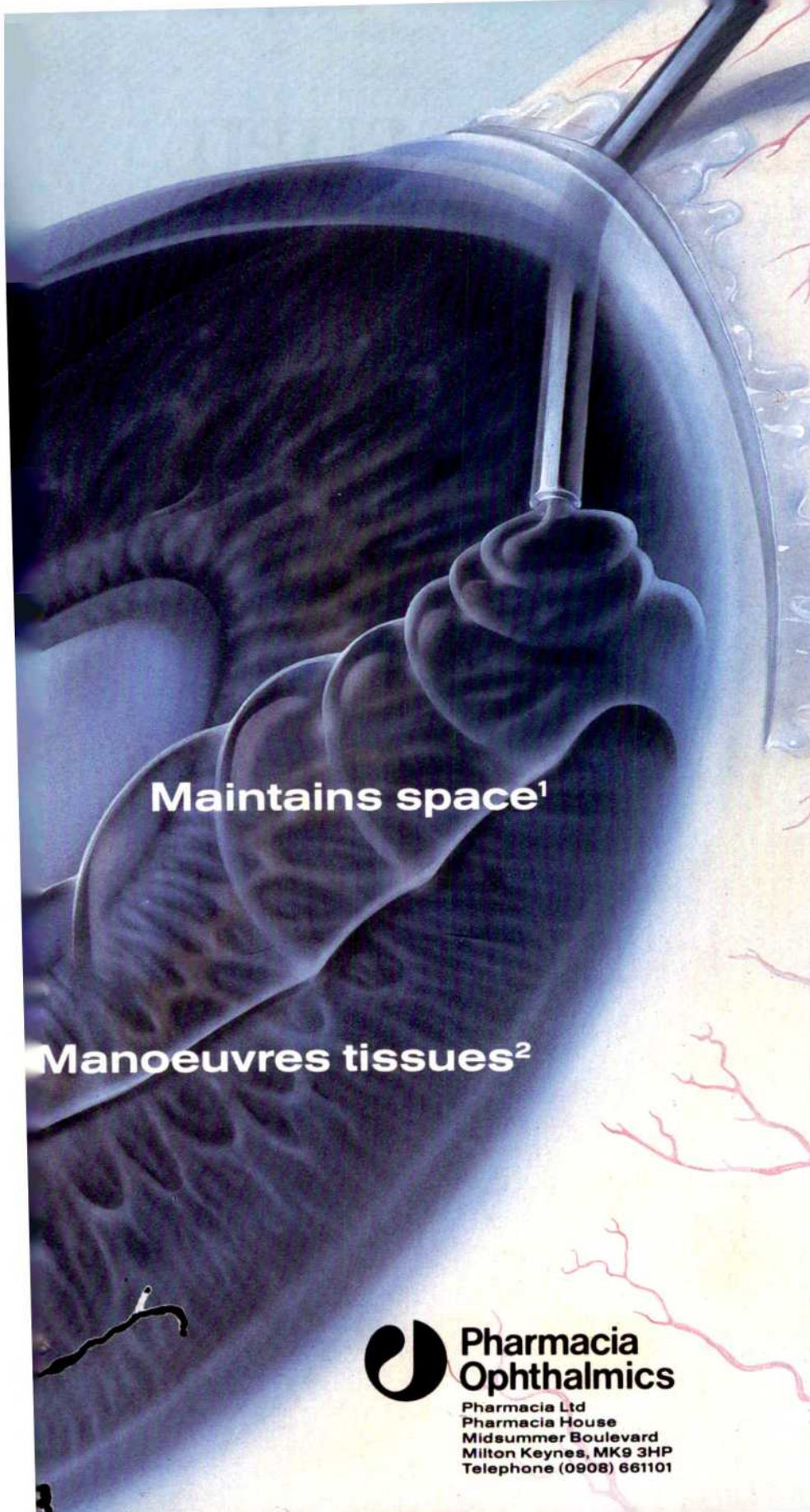
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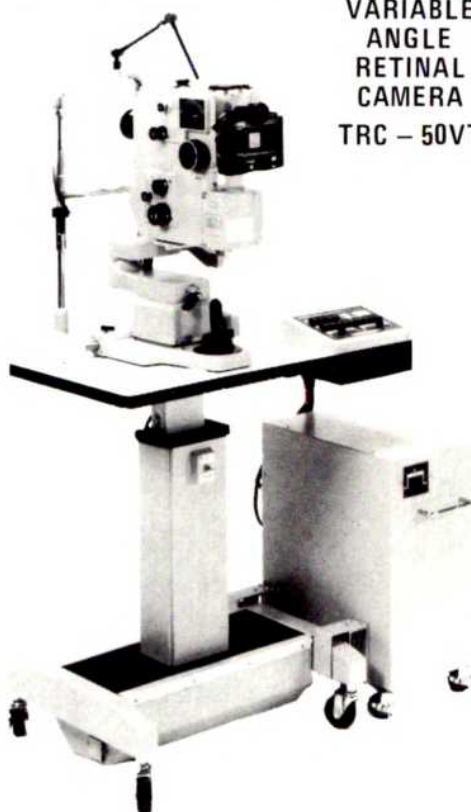
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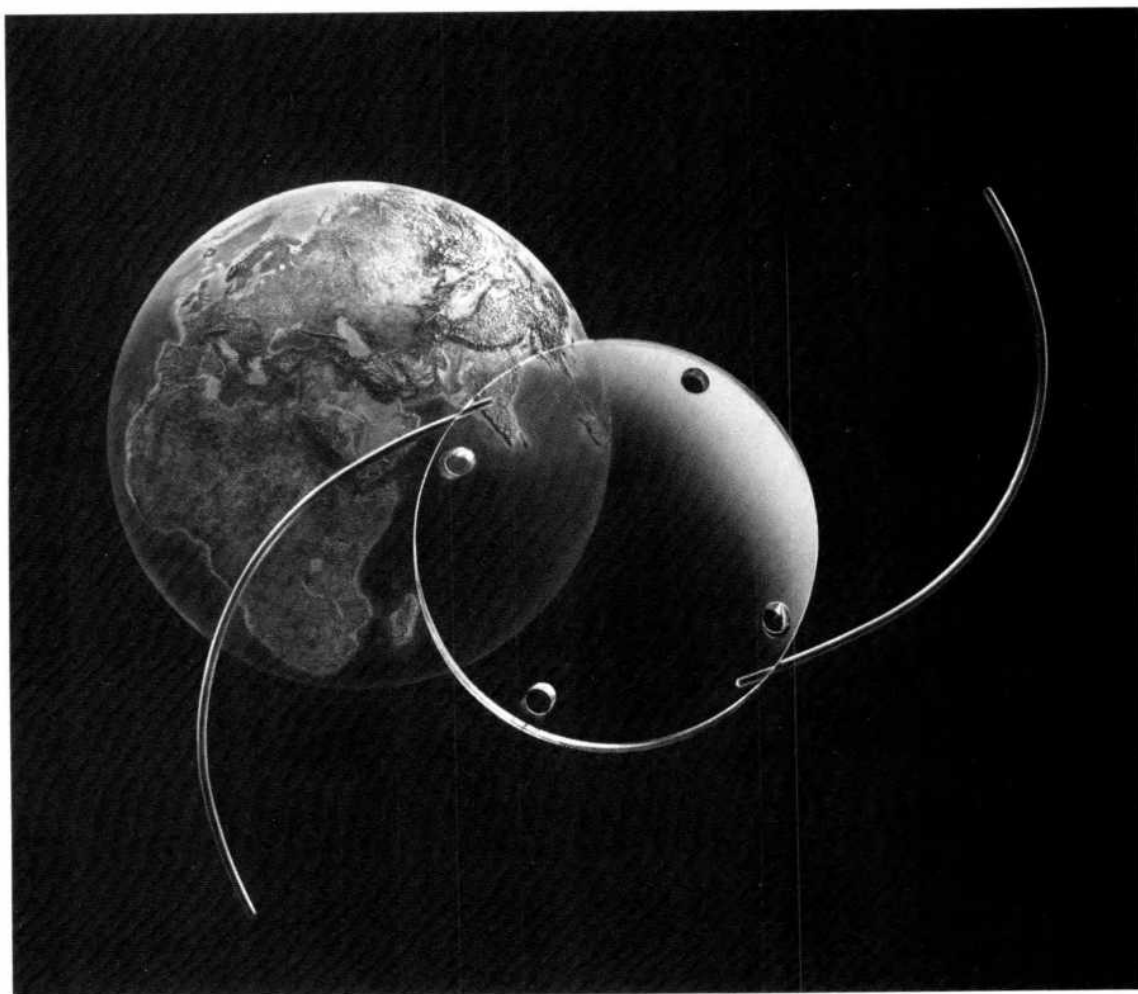
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Antibodies to herpes simplex virus type I in intraocular fluids of patients with acute retinal necrosis

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SUMMARY The intraocular fluids and sera from three patients with acute retinal necrosis (ARN) and from 120 age-matched controls were tested for the presence of antibodies to herpes simplex virus type I (HSV-I). Antibodies to HSV-I were detected in both intraocular fluids and sera of two cases, and in intraocular fluids alone in one case of ARN. Among 120 control patients undergoing routine intraocular surgery antibodies to HSV-I were detected in the sera of 85 (79.2%) but in the intraocular fluids of only two (1.7%). The presence of antibody within the eye may indicate local antibody production, antibody sequestration within the eye, or damage to the blood ocular barrier.

Recent interest in acute retinal necrosis (ARN) has drawn attention to its similarities with viral retinitis. The fundal appearances in ARN¹ are similar to the retinitis of herpes simplex virus infection in neonates² or the retinitis of cytomegalic inclusion disease.³

Histological evidence of viral infection in ARN was obtained by Cuthbertson *et al.* from an enucleated eye.⁴ Electron microscopy of the retina revealed viral particles of the herpes virus group. Serological studies in their patient showed the presence of antibody cross-reacting to all four types of the herpes virus. But no significant change in antibody titre was detected between the acute and convalescent sera. The authors suggested that the absence of rising antibody titre was due to localisation of the infection to the eye.

In two cases of ARN reported by Peyman *et al.*⁵ immunofluorescent staining of the vitreous aspirate was positive with antiherpes simplex virus polyclonal antibody. Vitreous cultures were negative for viruses. In one of these cases antibodies to herpes simplex virus, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, and variola were detected in the vitreous aspirate at low titres. However, to our best knowledge there have been no reports on the levels of these viral antibodies in intraocular fluids of unaffected patients.

We have studied antibodies to herpes simplex virus type I (HSV-I) in the blood and intraocular fluids of three patients with ARN. To establish a baseline we

also studied blood and intraocular fluid from control patients who were undergoing routine intraocular surgery with no evidence of HSV infection.

Materials and methods

A history of recent cold sores or genital ulceration was sought in each patient. A full ophthalmic and general examination was performed and included the recording of visual acuities and detection of any signs of intraocular inflammation in each eye. A full general examination was carried out, in particular with a search for evidence of oral or genital ulceration.

Two patients with ARN underwent vitrectomy for the treatment of complicated retinal detachment; samples of intraocular fluids were taken during this procedure. In the third case of ARN aqueous was sampled by a diagnostic tap of the anterior chamber.

In control patients intraocular fluid samples were taken peroperatively in such a way as to ensure that the samples were not contaminated by blood. Aqueous was collected from patients undergoing trabeculectomy or routine cataract extraction. When the anterior chamber was first opened, a sterile sponge measuring approximately 5×2×1 mm (Spontex Ltd) was saturated with aqueous (approximately 0.05 ml of fluid being collected). The sponge was then placed in a tightly stoppered dry plastic capsule and stored at +4°C until transferred to the laboratory.

Vitreous was collected via a two-way tap inserted in the aspiration line from the Ocutome vitrectomy

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Table 1 *HSV-I IgG antibodies detected in serum and intraocular fluids of three patients with acute retinal necrosis*

	Serum	Aqueous	Subretinal fluid	Vitreous
Patient 1	1:128		1:128	
Patient 2	0		1:16	1:16
Patient 3	1:32	1:32		

machine. A 1.0 ml insulin type syringe was used to withdraw a specimen from the tubing.

Subretinal fluid was collected by saturating a sterile sponge of the type used for the collection of aqueous.

Tears were collected from the conjunctival sac of the fellow eye during surgery by means of a dry cellulose sponge. In the patients with ARN and the patients undergoing routine intraocular surgery blood was withdrawn on the same day as intraocular fluid was collected. All specimens were tested for type specific antibodies to HSV-I by an indirect immunofluorescence test.⁶ Sera were tested for specific IgG at 1/16 or greater and for IgM at 1/8 or above. Other specimens were tested for specific IgG and IgA at 1/8 or greater.

Results

Antibody findings in three patients with acute retinal necrosis are shown in Table 1.

CASE 1

This 55-year-old woman was well until April 1982,

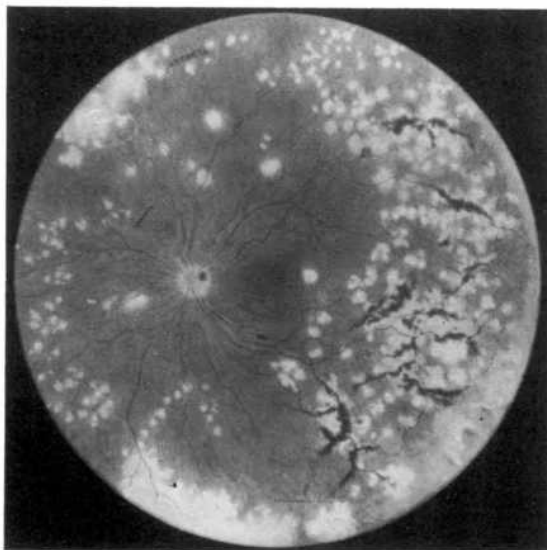


Fig. 1 Drawing of right fundus showing peripheral retinal necrosis and haemorrhage.

when she suddenly developed drowsiness and dysphasia. A diagnosis of herpes encephalitis was made, and she was treated with intravenous acyclovir and then systemic steroids, in reducing dosage. Three months later she complained of blurred vision in her left eye, and examination showed panuveitis with ARN (Fig. 1). Serum IgG to HSV-I was positive at a titre of 1:16.

She was treated with systemic steroids. Four weeks later she developed a total retinal detachment in her left eye (Fig. 2). A left vitrectomy, lensectomy, and silicone oil: fluid exchange were performed. Serum IgG antibody to HSV-I had risen to a titre of 1:128. HSV-I IgG was also present at a titre of 1:128 in subretinal fluid.

CASE 2

This was a 56-year-old woman who was well until she developed blurred vision in her right eye in September 1982. A diagnosis of ARN was made, and she was treated with intravenous acyclovir. Two months later a total retinal detachment developed in her right eye. A vitrectomy and gas: fluid exchange was performed. Serum IgG antibody to HSV-I was negative. However, IgG to HSV-I was present at a titre of 1:16 in the subretinal fluid and vitreous.

CASE 3

This was a 70-year-old man who was well until he developed pain in his left eye in September 1982. A diagnosis of ARN was made, and he was treated with intravenous acyclovir. IgG to HSV-I was present in his serum at a titre of 1:32. A diagnostic tap was performed on the anterior chamber, and IgG to HSV-I was found in the aqueous at a titre of 1:32.

We studied 120 consecutive patients undergoing routine anterior or posterior segment intraocular

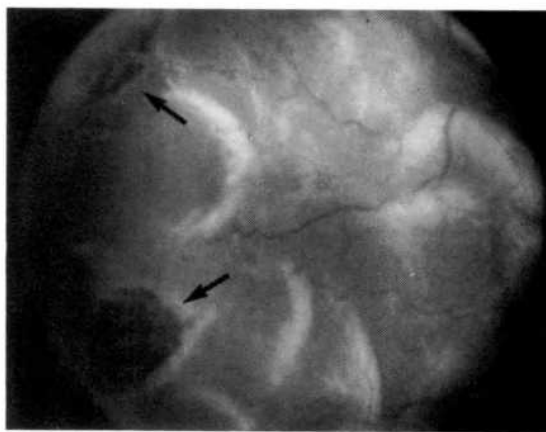


Fig. 2 Fundus photograph of peripheral retina showing retinal holes (arrows) and detached retina.

Table 2 HSV-1 IgG antibodies detected in serum, tears, and aqueous of 100 patients undergoing routine intraocular surgery

	No. negative	No. with antibodies to HSV-1
Serum	19	81
Tears	100	0
Aqueous	100	0

Table 3 HSV-1 IgG antibodies detected in serum, tears, and vitreous of 10 patients undergoing routine vitrectomy

	No. negative	No. with antibodies to HSV-1
Serum	3	7
Tears	10	0
Vitreous	9	1

Table 4 HSV-1 IgG antibodies detected in serum, tears, and subretinal fluid of 10 patients undergoing routine drainage of subretinal fluid

	No. negative	No. with antibodies to HSV-1
Serum	3	7
Tears	10	0
Subretinal fluid	9	1

surgery between 24 January 1983 and 31 July 1983. Their average age was 68 (range 14 to 90). There were 56 males and 64 females. Patients with a history of trauma or diabetes mellitus were excluded because of the increased incidence of vitreous haemorrhage in these conditions. None of the patients gave a history or showed signs of recent oral or genital ulceration and none had evidence of recent intraocular inflammation.

The patients studied may be considered in three groups depending on whether aqueous, vitreous, or subretinal fluid was collected in addition to tears and blood (Tables 2-4).

Aqueous was collected from 100 patients. No antibodies to HSV-1 were found in aqueous or tears. Antibodies to HSV-1 were found in the sera of 81 (Table 2).

Vitreous was collected from 10 patients. Serum antibody to HSV-1 was found in seven patients. No antibody to HSV-1 was found in tears. In one patient IgG to HSV-1 was found at a titre of 1:8 in the vitreous. Concurrent serum IgG was 1/64 (Table 3).

Subretinal fluid was collected from 10 patients. In seven patients serum antibody to HSV-1 was positive. In none of the tears collected were antibodies to HSV-1 present. In one patient subretinal fluid antibody to HSV-1 was present at a titre of 1:32;

concurrent serum titre in this patient was also 1:32 (Table 4).

Discussion

We found antibody to HSV-1 in intraocular fluids of three patients with ARN and in two out of 120 (1.7%) of controls.

We consider that there are four possible explanations for the presence of antibody in intraocular fluids. First, the antibody may be produced within the eye. Secondly, it may be produced elsewhere but sequestered in the eye. Thirdly, it may leak from the serum when the blood-ocular barrier is damaged. Fourthly, it may leak into the eye during the sampling procedure.

The presence of higher antibody levels in the aqueous than in the serum has been cited as proof of local antibody production within the eye. Felberg *et al* reported five cases of ocular toxocariasis in which antibody titres to *toxocara canis* in the aqueous were significantly higher than the serum.⁷ They assert that the presence of plasma cells in the eosinophilic abscess which characterises nematode endophthalmitis is suggestive of local production of antibody.

However, there are difficulties making direct comparisons between serum and aqueous without taking account of the different concentrations of IgG. Pedersen and Lorentsen-Styr compared aqueous and serum concentrations of antibody against *Toxoplasma gondii* in 10 patients with active retinochoroiditis.⁸ According to a formula derived from Desmonts,⁹ they calculated the aqueous humour antibody coefficient:

$$\text{Coefficient} = \text{antibody titre} \frac{\text{aqueous}}{\text{serum}} \times \text{globulin} \frac{\text{serum}}{\text{aqueous}}$$

A titre greater than 1 indicated that aqueous humour globulins were richer in toxoplasma antibodies than the serum. In six out of 10 patients the antibody aqueous humour coefficient was significantly raised. This finding suggests local antibody production within the eye.

There have also been reports of autoantibody detected within the aqueous but not in the serum of patients with uveitis. In two patients with chronic anterior uveitis and Still's disease antinuclear antibodies were present in the aqueous but not in the blood.¹⁰ Rheumatoid factor was detected in aqueous but not serum of five patients with endogenous uveitis.¹¹ However, in all these circumstances it is possible that antibody had been sequestered in the eye rather than produced there.

There is indirect evidence of leak of antibody across a damaged blood ocular barrier. The uveal

vessels have been shown to exert a degree of selectivity when albumin-bound trypan blue and colloidal carbon were used as markers.¹² The integrity of this barrier could be compromised after local application of histamine.¹³ A similar leak may occur after any episode of intraocular inflammation. Pedersen and Lorentsen-Styr noted a high level of IgG in the aqueous of a patient with active uveitis.⁸ Antibody leak would certainly explain the finding of antibody to HSV-I in two patients with ARN (cases 1 and 3). In one patient, case 2, antibody to HSV-I was not detected in the serum, implying there was local antibody production or sequestration. However, in this case the titre of antibody in the subretinal fluid and vitreous was low.

Though antibody to HSV-I was present in the sera of 95 out of 120 (79%) patients undergoing routine intraocular surgery, it was present in the intraocular fluids of only two (1.7%) patients. This makes it highly unlikely that the detection of antibody in intraocular fluids was due to contamination during the sampling procedure.

In conclusion, we consider that antibody in intraocular fluid may result from local antibody production or sequestration or damage to the blood ocular barrier. To establish which process is responsible studies of intraocular fluids in inflamed eyes are required. The presence of antibody to HSV-I in the intraocular fluid of patients with ARN is highly suggestive evidence that this virus causes this disease.

We thank the surgeons at Moorfields for allowing us to study their cases, Mr Richard Dewhurst for preparation of the illustrations, and Miss Josephine Lacey for secretarial assistance.

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IgG and IgA immune response against klebsiella in HLA-B27-associated anterior uveitis

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SUMMARY Enteric infections with Gram-negative bacteria are thought to play an important part in HLA-B27-associated disease such as Reiter's syndrome and reactive arthritis. But the role of bacterial infections in HLA-B27-positive ankylosing spondylitis (AS) and acute anterior uveitis (AU) is still controversial. A special interest has recently been devoted to the role of klebsiella infection in HLA-B27-associated disease. We studied the humoral immune response against a 'cross-reactive' strain of *Klebsiella pneumoniae* in 62 patients with anterior uveitis and 33 healthy controls. The anterior uveitis patients were subdivided into 25 HLA-B27-negative patients without AS (B27⁻ AU⁺ AS⁻), 17 HLA-B27-positive patients without ankylosing spondylitis (B27⁺ AU⁺ AS⁻), and 19 HLA-B27-positive patients with ankylosing spondylitis (B27⁺ AU⁺ AS⁺). Total serum IgA was higher in patients than in controls in both the B27⁺ AU⁺ AS⁺ and B27⁺ AU⁺ AS⁻ patients but not in the B27⁻ AU⁺ AS⁻ group. No abnormalities were observed in the total serum IgG levels. The level of both the IgG and IgA klebsiella antibodies did not differ in the various patient groups tested as compared with the controls. Comparisons between the patient groups showed that the IgG anti-klebsiella response was higher in B27-positive patients without AS than in those with AS. These results suggest that stimulation of mucosal surfaces may play a role in HLA-B27-associated anterior uveitis. Whether klebsiella organisms are involved in this stimulation remains unclear.

Enteric infections with certain Gram-negative bacteria are thought to play an important role in HLA-B27-associated disease.^{1,2} Strong though circumstantial evidence to support the role of Gram-negative bacteria in the initiation of HLA-B27-associated disease is found in Reiter's syndrome and reactive arthritis.³ The role of enteric infections in the pathogenesis of ankylosing spondylitis and HLA-B27-positive acute anterior uveitis is still not clear. Some groups have found an increase in klebsiella in the faeces of patients with anterior uveitis,⁴ whereas others were unable to confirm these findings.^{5,6} Similar controversial findings have been obtained in ankylosing spondylitis patients.^{7,8}

Several theories have been proposed to explain the role of Gram-negative bacteria in the pathogenesis of HLA-B27-associated disease. Cross-reactions

between klebsiella and HLA-B27 antigens⁹ or ligand receptor interactions between bacterial antigens and HLA-B27¹⁰ have been found by some workers but were not reproduced in other laboratories.^{11,12}

Increased serum IgA levels in ankylosing spondylitis^{13,14} suggest that mucosal infections may play a part in the course of the disease. Other studies have shown that klebsiella-specific IgA antibodies were increased in ankylosing spondylitis, and the antibody levels were shown to be correlated with disease activity.¹⁵ Whether the IgA response against klebsiella organisms is also altered in HLA-B27-associated acute anterior uveitis has not been thoroughly investigated until now and was therefore the purpose of the study described here. The results show that, although total serum IgA levels are increased in HLA-B27-positive anterior uveitis, the relative amount of IgA anti-klebsiella antibodies is decreased in comparison with controls. The IgG anti-klebsiella response was higher in B27-positive

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patients without ankylosing spondylitis than in patients with ankylosing spondylitis.

Materials and methods

A total of 62 patients with anterior uveitis from the Ophthalmology Departments of the Erasmus University of Rotterdam, University of Amsterdam, and Free University of Amsterdam were included in this study. Serum was obtained from all patients during while the disease was active and from 33 healthy members of our institute.

All patients were seen by a rheumatologist. Physical examination included measuring the flexion capability of the lumbar spine by the modified technique of Schober (normal shift >5 cm) and examination of spinal movement in three planes. Chest expansion was determined at nipple level in males and below the breasts in females (normal shift >5 cm). X-rays of the sacroiliac joints were taken in anteroposterior view of the pelvis in a 25° craniocaudal direction. All radiographs were examined without the investigator's knowing which patient's radiograph he was observing. The diagnosis of ankylosing spondylitis was made according to the New York criteria.¹⁴

All patients were typed for the HLA-B27 antigen according to the National Institute of Health technique with four different commercially available HLA-B27 typing sera (Behring, Marburg, W Germany, one serum; Biotest, Frankfurt, W Germany, three sera. Patients and controls were subsequently divided in four groups consisting of healthy controls, B27-positive anterior uveitis patients with ankylosing spondylitis, B27-positive anterior uveitis patients without ankylosing spondylitis, and HLA-B27-negative anterior uveitis patients.

Total IgA and IgG serum levels were determined by radial immunodiffusion with precipitating rabbit antisera and a human standard serum containing 125 international units of IgG and 116 international units of IgA obtained from the Central Laboratory of Blood Transfusion (Amsterdam). IgA and IgG antibodies against klebsiella antigens were determined by an ELISA as described by Trull *et al.*¹⁵ with minor modifications.

The klebsiella K43 'cross-reactive' strain (obtained from Dr A F Geczy, Sydney, Australia) was grown in a Koser's citrate broth with 1% inositol¹⁷ overnight at 37°C. The protein content of the culture filtrate, obtained after centrifugation and passage through Millipore filters was measured by the Folin method using bovine serum albumin (BSA) as a standard. The filtrate was diluted to a protein concentration of 7.5 µg/ml in phosphate buffered saline, and micro-

cuvettes (Gilford, Cleveland, Ohio) were coated overnight at 37°C with 300 µl per cuvette. After being coated the cuvettes were washed three times with phosphate buffered saline containing 0.1% Tween (PBS 0.1% Tween). Subsequently 250 µl serum samples, diluted 1/25 in PBS 0.1% Tween containing 2 mg/ml BSA, were incubated for 2 hours at 37°C. After being washed three times with PBS 0.1% Tween the cuvettes were incubated with a 1/2000 dilution of heavy chain specific peroxidase conjugated goat anti-human IgA or IgG antibody respectively for 1 hour at 37°C (Nordic, Tilburg, The Netherlands). After being washed three times with PBS 0.1% Tween, bound peroxidase labelled antibody was developed at room temperature by adding 350 µl ABTS solution (0.16 mM 2,2-azino-di-3-ethyl-benzthiazoline-6-sulphonate, Boehringer, Mannheim, W Germany; 0.15% H₂O₂ in 0.05 M citric acid, pH 4.0). The reaction was stopped by adding 50 µl 10% sodium dodecylsulphate to each cuvette. The green reaction product was measured in a spectrophotometer (EIA, Gilford, Cleveland, Ohio, USA) at 405nm. As a standard a serum sample was used from a pool of normal human sera. This standard was considered to contain 10 ELISA units of IgG and of IgA anti-klebsiella antibodies respectively.

Statistical analysis of the data was by Student's *t* test.

Results

The sex and age distributions of the various patient groups and controls are shown in Table 1. Serum IgA was significantly increased in the HLA-B27-positive anterior uveitis patients also suffering from ankylosing spondylitis as compared with controls ($p < 0.001$). The IgA levels in patients with HLA-B27-positive anterior uveitis without ankylosing spondylitis was somewhat less but still significantly ($p < 0.025$) increased as compared with controls. Other comparisons between the groups investigated did not show significant differences.

The IgA response against klebsiella was not statistically different between the groups of patients tested and controls. When the relative amount of IgA anti-klebsiella antibodies was calculated (ratio of anti-klebsiella IgA divided by total IgA) for each patient, it was found that the HLA-B27-positive anterior uveitis patients with ankylosing spondylitis had a significantly ($p < 0.01$) decreased ratio (Table 1). The ratios in the other patient groups were not different from those of the controls.

Serum levels of IgG (Table 2) were not altered in the patient groups investigated when compared with controls. Further, no differences were observed in the IgG anti-klebsiella antibodies between the

Table 1 Total serum IgA and IgA and klebsiella in anterior uveitis*

	n	Female	Male	Mean age	Total IgA	Anti-klebsiella IgA	Ratio
Controls	33	19	14	34	109±59	9.5±7.5	0.103±0.086
B27 ⁺ AU ⁺ AS ⁺	19	8	11	33	181±76†	7.2±3.7	0.050±0.037‡
B27 ⁺ AU ⁺ AS ⁻	17	7	10	33	154±68‡	9.0±6.0	0.073±0.069
B27 ⁻ AU ⁺ AS ⁻	25	16	9	42	119±51	8.9±5.8	0.086±0.055

*Total IgA levels are expressed as international units, whereas anti-klebsiella IgA is expressed in local ELISA units. Data represent the mean ± standard deviation. Ratios represent anti-klebsiella IgA divided by total IgA as calculated for each individual.

†p<0.001 (compared with controls)

‡p<0.025 (compared with controls)

§p<0.01 (compared with controls)

patient groups and controls. The IgG anti-klebsiella response was, however, significantly higher in the B27⁺ AU⁺ AS⁻ group as compared with the B27⁺ AU⁺ AS⁺ group (p<0.01). Calculation of the ratio between klebsiella IgG antibodies and total serum IgG showed no differences between the patient groups and controls (Table 2). A comparison of these IgG ratios between the patient groups showed that the B27⁺ AU⁺ AS⁺ patient group had relatively less IgG anti-klebsiella antibodies compared with the B27⁺ AU⁺ AS⁻ group.

Discussion

This study shows that the total serum IgA level is increased in patients with HLA-B27-positive anterior uveitis. Similar findings were recently reported by McCoy *et al.*¹⁴ These observations indicate that antigenic mucosal stimulation may play a part in the pathogenesis of HLA-B27-associated anterior uveitis. Within this patient group those patients who also had ankylosing spondylitis had higher IgA levels than those without. Raised total IgA levels in ankylosing spondylitis have been reported elsewhere and were shown to be correlated with disease activity.¹⁴ In ankylosing spondylitis it has also been shown that IgA antibodies against klebsiella were increased in patients with active disease.¹⁵ Using a similar technique, we were unable

to find an alteration in the IgA response against a 'cross-reactive' *Klebsiella pneumoniae* strain in HLA-B27-positive uveitis patients. These findings indicate that the alleged stimulatory effect on the IgA synthesis seen in B27-positive uveitis patients does not result in a parallel increase in the IgA anti-klebsiella antibodies.

Several explanations are possible for these observations. First, it can be supposed that klebsiella organisms are not involved in the course of the disease at all, but that other mucosal inflammatory disorders, infectious or non-infectious, are the cause of the raised IgA levels in these patients. On the other hand it could be argued that only one klebsiella serotype was investigated in the study described here and that, furthermore, only the immune response against soluble bacterial antigens was tested. The strain used (obtained from Dr A F Geczy) has been found to contain antigens which may have an important role in HLA-B27-associated diseases.¹⁶ It has been shown to be a producer of 'modifying factor', a protein which is considered to be present on the lymphocyte membrane of most HLA-B27-positive ankylosing spondylitis patients and which was shown to interact with the lymphocytes of HLA-B27-positive healthy individuals. We may wonder whether any of this 'modifying factor' was present in the klebsiella culture filtrate used for coating the microcuvettes. Because for the ELISA technique the K43 strain was grown in a minimum essential medium, it is possible that certain bacterial antigens were not present in the culture filtrate, for it is known that the phenotypical expression of some bacterial antigens requires specific growth conditions.

A second possibility is that enteric infections with klebsiella organisms may be involved in the pathogenesis of the disease, but that this does not result in a stimulation of the klebsiella-specific immune response but rather in a polyclonal IgA stimulation.¹⁷ The hypothesis that a mucosal stimulation is involved is suggested by the fact that only the IgA levels but not the IgG levels are raised in the B27-positive uveitis patients.

Table 2 Total serum IgG and IgG anti-klebsiella in anterior uveitis*

		Anti-Klebsiella IgG	Ratio
Controls	146±44	7.2±5.7	0.050±0.044
B27 ⁺ AU ⁺ AS ⁺	166±46	5.4±2.7	0.035±0.019
B27 ⁺ AU ⁺ AS ⁻	155±74	10.7±7.2†	0.079±0.054‡
B27 ⁻ AU ⁺ AS ⁻	143±43	8.1±6.0	0.066±0.065

*Total IgG levels are expressed as international units, whereas anti-klebsiella IgG is expressed in local ELISA units. Data represent the mean ± standard deviation. Ratios represent anti-klebsiella IgG divided by total IgG as calculated for each individual.

†p<0.001 (B27⁺ AU⁺ AS⁺ vs. B27⁺ AU⁺ AS⁻)

‡p<0.005 (B27⁺ AU⁺ AS⁺ vs. B27⁺ AU⁺ AS⁻)

Arguments which indicate that klebsiella organisms or cross-reactive bacteria do play a part in HLA-B27-associated uveitis stem from our finding that IgG levels against the klebsiella antigens were twice as high in the patients without ankylosing spondylitis than in those with ankylosing spondylitis. In conclusion, the findings reported here do not conclusively show an involvement of *Klebsiella pneumoniae* in the pathogenesis of HLA-B27-associated anterior uveitis, but they do suggest that factors resulting in an increased serum IgA play a part in this disease.

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An in-vitro morphological study of Q-switched neodymium/YAG laser trabeculotomy

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SUMMARY Laser trabeculotomies produced by directing a pulsed neodymium/YAG laser beam at specimens of human anterior chamber angle obtained post mortem or after enucleation were studied by light microscopy and by scanning and transmission electron microscopy to assess the dimensions of the openings created in the trabecular meshwork, their penetrance to the canal of Schlemm, and the extent or absence of laser induced cellular damage in immediately adjacent tissue. A pulse duration of 40–50 ns at energy levels of around 30 mJ was used and the laser cavity carefully tuned to give a Gaussian spatial mode pattern. Openings in the trabecular meshwork typically of 100 μ m in diameter and penetrating through to the canal of Schlemm could be regularly created with only minimal damage to adjacent tissue as judged by transmission electron microscopy. The information so gained may be useful in determining the parameters required for successful laser trabeculotomy as a treatment for primary open-angle glaucoma.

A Q-switched neodymium/YAG laser system has been developed with the intention of performing internal laser trabeculotomies as a treatment for primary open-angle glaucoma. The ultimate aim of such a treatment would be to create dimensionally controlled, precisely positioned channels through the diseased and hyalinised meshwork without inducing a tissue repair response in the adjacent trabecular tissue or within the lumen of Schlemm's canal.

This report describes in-vitro experiments using the Nd/YAG system on samples of the chamber angle from human eyes, obtained post mortem or after surgical enucleation. Some samples were fixed in glutaraldehyde before the laser treatment so that control over tissue autolysis was achieved; others were not fixed, in order to assess any alteration of the response to the laser pulses in the absence of membrane stabilisation by the fixative.

The laser operating parameters were chosen after preliminary experiments¹ had indicated the appropriate levels required to produce channels of suitable dimensions (c. 100 μ m diameter). The

effects of the laser pulses were studied initially by scanning electron microscopy, as this was a relatively quick way to detect the presence and location of laser holes and to study their configuration and dimensions.

Selected tissue samples were then retrieved for resin embedding for light and transmission electron microscopy in order to study the laser damage at a cellular level and to reinforce the dimensional data obtained by scanning electron microscopy.

Materials and methods

LASER OUTPUT AND DELIVERY SYSTEM

The laser system used was the Hyper YAG 2000 produced by J K Lasers Ltd. It was operated at its fundamental wavelength of 1.06 μ m. The Q-switched pulse durations were between 40 and 50 ns, as measured by a fast photodiode detector (Centronic APD 05 4R). Fig. 1a shows the temporal intensity profile of a typical pulse.

The laser output was channelled into its fundamental transverse mode, which offered two advantages: (1) the theoretical limit for the focused beam diameter is smaller than for other modes, and (2) the

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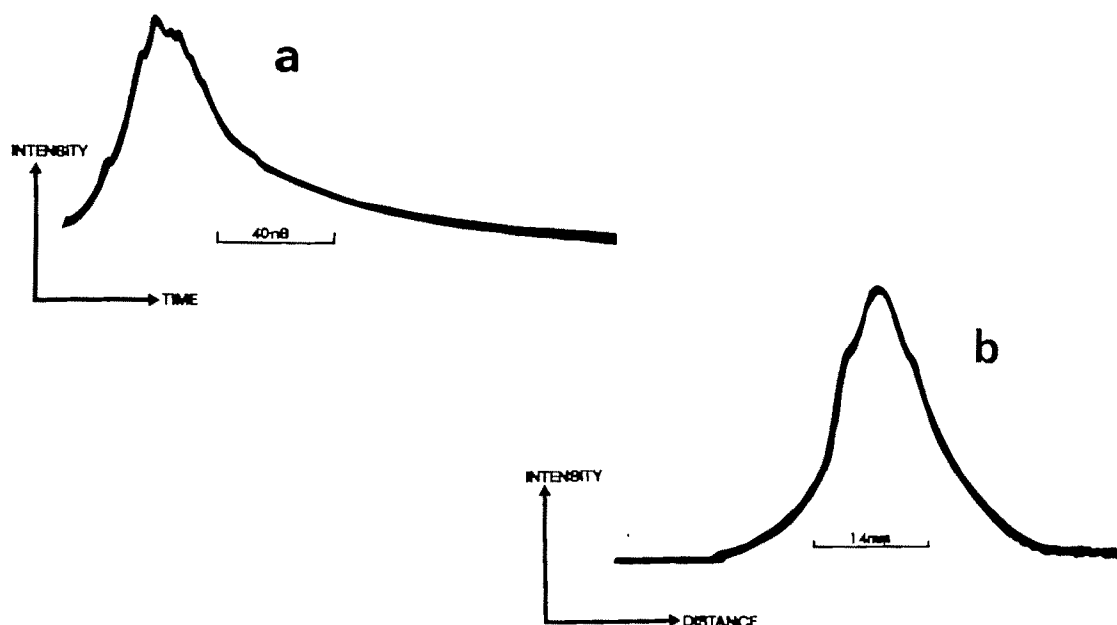


Fig. 1 Temporal (a) and spatial (b) intensity profiles recorded from typical Q-switched Nd/YAG pulses.

variability in the pattern of the intensity from one pulse to another is minimised. The mode pattern of the unfocused neodymium/YAG beam was periodically recorded with a photodiode array detector (EG and G Reticon RL512G) so that adjustments could be made to the laser cavity optics, if necessary, to regain the fundamental mode (indicated by a smooth Gaussian profile). This also permitted measurements of beam diameter to be made.* The spatial intensity profile of a typical pulse, as recorded by the array, is shown in Fig. 1b.

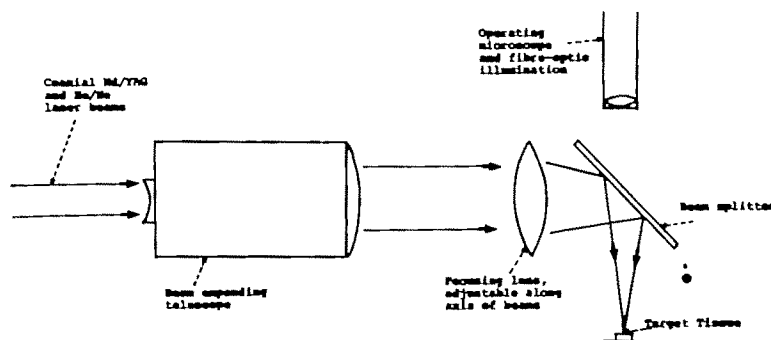
The experimental arrangement used for these

studies is shown in Fig. 2. A low-power continuous wave helium neon laser beam was directed coaxially into the invisible Nd/YAG beam to mark its path and allow visual focusing. The delivery system supplied with the Nd/YAG laser was removed, and the two beams were delivered to the target through a beam expanding telescope and a single focusing lens. A beam splitter was positioned to reflect all of the Nd/YAG beam and a proportion of the HeNe beam through 90° while allowing the through passage of visible light for observations via an operating microscope.

The focusing lens was mounted on a micropositioning stage so that its position along the axis of the beams could be altered and set with precision. This set the position at which the HeNe beam was focused relative to the surface of the target. Since it is

*The laser beam diameter entering the beam expanding telescope was 1.5 mm, the diameter leaving it was 9.0 mm, and the converging angle of the beam leaving the final focusing lens was 6° . The estimated power density over the focal spot, which was below $50 \mu\text{m}$ in diameter, was of the order of 10^8 Watt/mm^2 .

Fig. 2 Schematic diagram of experimental apparatus



theoretically likely that the Nd/YAG focal point would not exactly coincide with that of the HeNe beam, many of the Nd/YAG pulses were fired with the HeNe focus at points other than the target surface—that is, up to 4 mm beyond the surface of the tissue and 2 mm in front of it.

The laser pumping voltage, which determined the pulse energy, was set at 750 V for all the pulses fired in this study. The actual pulse energy output was measured with a photodiode-based energy monitor (J K Lasers Ltd) and was in the range 30.0 mJ to 32.4 mJ, corresponding to pulse power of the order of 10⁶ Watts. One, two, or three pulses were fired at each target site, allowing at least 10 s to elapse between pulses. The details are shown in Table 1.

TISSUE

Wedges of tissue comprising the outflow system and the limbal regions of cornea, anterior sclera, iris, and ciliary body were dissected from the excised anterior segments of five enucleated human eyes. Human tissue was preferred because of its distinctive morphology vis-à-vis that of other primates. Details of the age of the donor, and the treatment of the tissue are given in Table 2, but, to summarise, most of the tissue was obtained post mortem from elderly donors, approximately half the material was fixed in glutaraldehyde before laser treatment, and the rest was fixed immediately after laser treatment. All the tissue was kept wet until immediately before laser treatment to minimise drying artefacts. The scleral base of each tissue wedge was glued to a small metal block, and the uveal surface of the meshwork was exposed to the Q-switched Nd/YAG pulses.

MORPHOLOGICAL METHODS

The first stage of the morphological study of the

effects of the laser pulses on the tissue was scanning electron microscopy (Jeol JSM T200), for which the samples were prepared by critical point drying. Measurements of the areas of meshwork surface visibly damaged by the laser were made by image analysis (Micro Measurement Ltd, Optomax).

Some of the specimens that showed clear laser holes by scanning electron microscopy were then reprocessed for resin embedding by transfer through amyl acetate, ethanol, and a 50/50 mix of propylene oxide and resin (either Araldite or Transmit). Semithin (1 µm) serial sections were cut and stained with toluidine blue for light microscopy. Measurements of the maximum diameter of each hole were made from photomicrographs at known magnifications. Ultrathin sections (60–80 nm) were cut from selected specimens, stained with uranyl acetate and lead citrate, and studied by transmission electron microscopy (Philips EM301).

Results

Table 1 summarises the results in terms of the laser holes made in each tissue sample under different operating conditions. It was found that 30 mJ pulses could make clearly defined holes in both fixed and fresh trabecular tissue. Holes could be made in fixed tissue when the tissue surface was positioned anywhere between 1 mm in front of the plane of focus for the helium neon beam and 3 mm beyond it. Determining the focus of the HeNe beam on the meshwork surface was found to be much more difficult for fresh tissue than for fixed, probably because the fresh tissue was so transparent that very little light was scattered back from its surface. It should be noted that this might be ultimately a problem in vivo, in the clinical application of this laser treatment. However,

Table 1 Conditions of laser treatment and corresponding effects

Code No of eye	Tissue state	No of sites treat- ment	No of pulses per site made	No. of holes made	Range of positions beyond (b) or in front of (f) the HeNe focus for which holes were made
1	Fixed	20	1	17	3 mm b to 0.5 mm f
1	Fixed	6	2	4	3 mm b to 0.5 mm f
1	Fixed	1	3	1	1 mm b
2	Fixed	6	1	2	3 mm b to HeNe focus
3	Fixed	1	1	1	At HeNe focus
3	Fixed	5	2	3	1 mm b to HeNe focus
4	Fresh	5	1	2	1 mm b to HeNe focus
4	Fresh	6	2	3	2 mm b to 1 mm b
5	Fresh	4	1	3	0.6 mm b to 0.5 mm b
5	Fresh	11	2	6	0.6 mm b to 0.25 mm b
3	Fresh	1	1	0	—
3	Fresh	12	2	8	1.5 mm b to HeNe focus

Table 2 Source and treatment of tissue

Code number of eye	Age of donor (years)	Treatment of tissue
1	64	Eye enucleated post mortem and fixed in glutaraldehyde
2	64	Eye enucleated post mortem and fixed in glutaraldehyde
3	Over 60	Eye enucleated post mortem, half fixed in glutaraldehyde, and half laser treated unfixed within 3 hours
4	70	Eye enucleated post mortem and laser treated unfixed within 3 hours
5	76	Eye enucleated from living donor (because of choroidal melanoma) and laser treated unfixed within 1½ hours

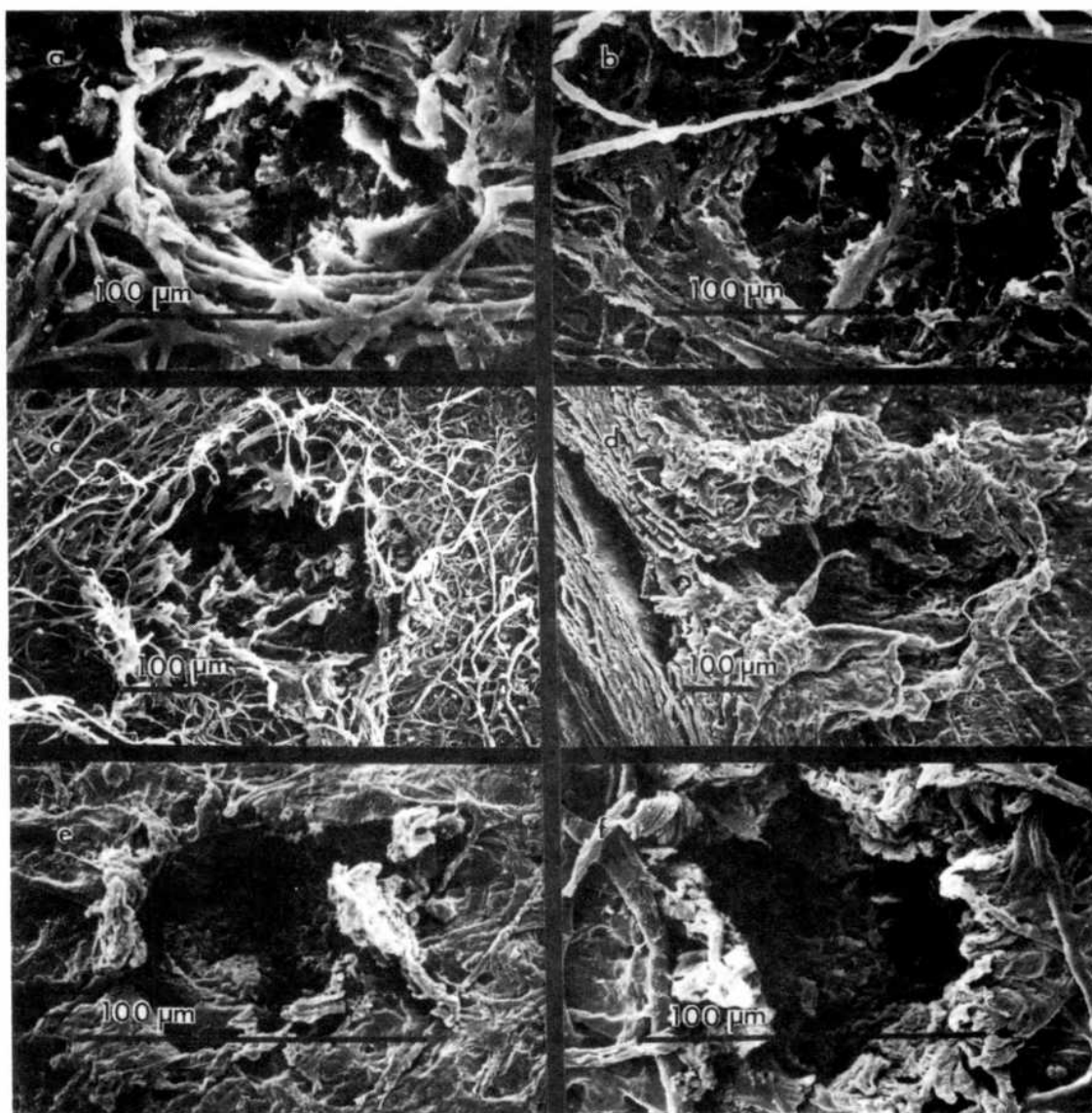


Fig. 3 Scanning electron micrographs of laser holes, made under the following conditions: (a) 2 pulses into fresh tissue at 1.0 mm beyond the HeNe focus; (b) 2 pulses into fresh tissue at 0.25 mm beyond the HeNe focus; (c) 2 pulses into fresh tissue at 0.60 mm beyond the HeNe focus; (d) 2 pulses into fresh tissue at 0.30 mm beyond the HeNe focus; (e) 1 pulse into fresh tissue at 1.0 mm beyond the HeNe focus; (f) 2 pulses into fresh tissue at 0.5 mm beyond the HeNe focus.

in the present investigation it was found that the effective depth of focus for fresh tissue was approximately half that for fixed tissues.

Scanning electron micrographs of a selection of the laser holes are shown in Fig. 3. Each hole, in fixed or fresh tissue, was sharply outlined by truncated trabecular beams and sometimes by a folded-back rim of tissue. This morphology could be interpreted

as an effect of concentrated explosions at or just below the surface. There was considerable variation in the size of the holes. The morphometric studies (image analysis) showed that 75% of the holes made had areas in the range 1500 to 15 000 (μm^2). There was no significant correlation between the internal area of the hole and two variables of the laser delivery system—the tissue position relative to the HeNe

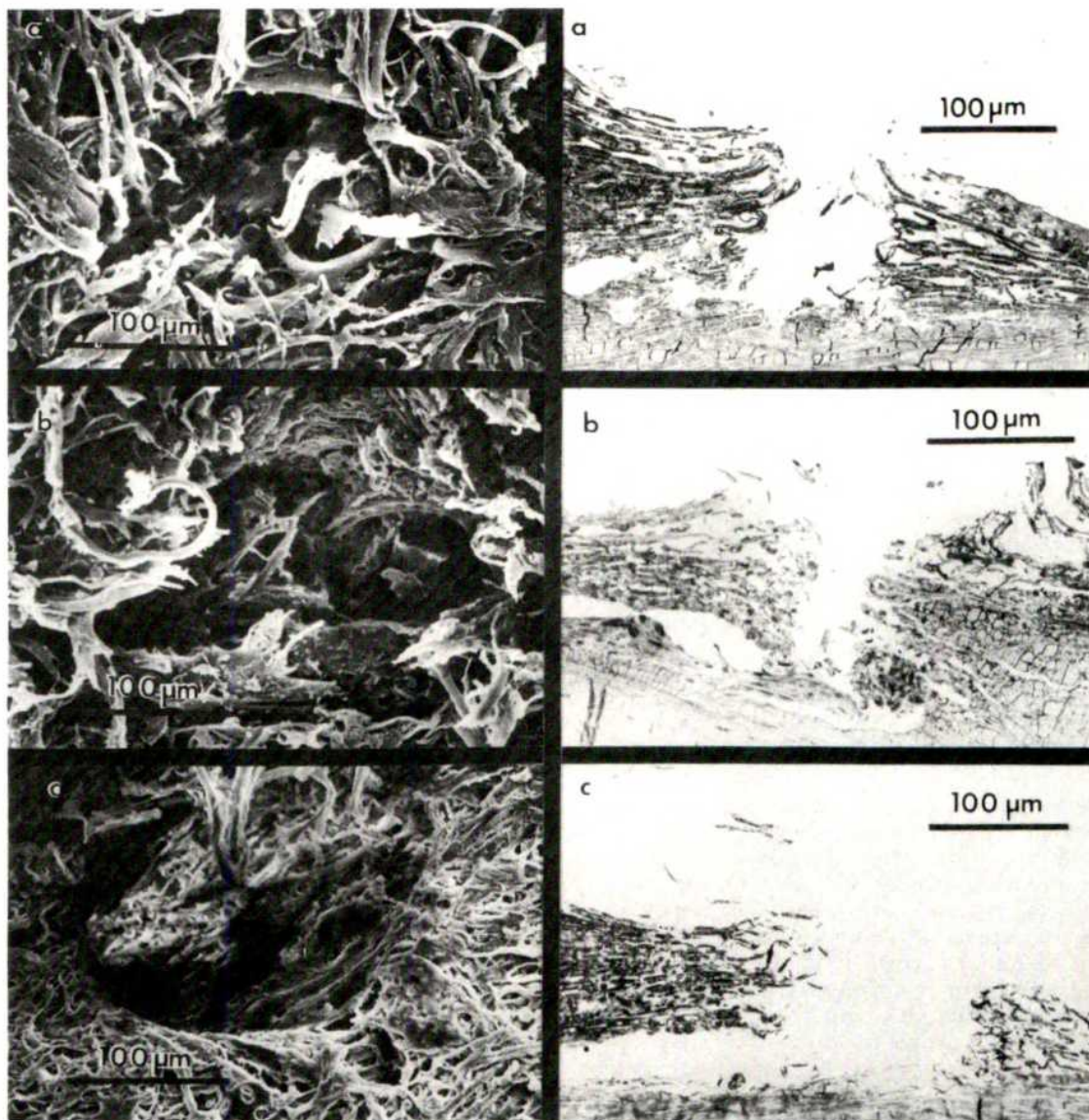


Fig. 4 Scanning electron micrographs and photomicrographs of three laser holes made under the following conditions: (a) 2 pulses into fresh tissue at 2.0 mm beyond the HeNe focus; (b) 1 pulse into fresh tissue positioned at the HeNe focus; (c) 1 pulse into fresh tissue at 0.5 mm beyond the HeNe focus.

focus, and the number of pulses fired per site. Even the holes created under apparently identical conditions varied considerably. For example, three holes made in fixed tissue from the same eye, positioned 1 mm beyond the HeNe focus, and receiving a single pulse at each site, had areas of 3360, 4100 and 11 300 (μm)² respectively.

Light microscopy of tissue sections stained with toluidine blue showed that many of the holes made by

laser pulses extended through the full thickness of trabecular meshwork into Schlemm's canal. This was often not obvious by scanning electron microscopy, even by examination of stereopairs of micrographs in a stereoviewer. Fig. 4 shows corresponding pairs of scanning electron micrographs and light micrographs of three of the lasered specimens. The clean-cut edges of the laser holes are also more obvious in the photographs of the 1 μm tissue sections. Measure-

ments of hole diameter taken from such photographs were typically approximately 80% of corresponding measurements taken from scanning electron micrographs.

Transmission electron microscopy of the tissue around the holes produced by the laser showed variable changes which appeared to be dependent on both the induced structural damage and on the state of autolysis. In those eyes in which cellular preservation could be considered optimum (specimens 1 and 5) it was possible to establish normal cell morphology at distances between 50 and 200 μm from the edge of the hole (Fig. 5 and 6). Within 50 to 100 μm from the edge of the hole some cells showed obvious disruption of the cell membrane (Fig. 5b) with release of cytoplasmic constituents. The cell damage was, however, patchy, and intact cells were found within 35 μm (Fig. 6b) from the edge of the hole. Many of the trabecular beams at the edge were denuded of endothelial cells and trabecular core material was loosened. The beams were disrupted and bent over a distance of about 25 μm and fragments of trabecular cores were present in the interspaces. There was no apparent thermal damage to the constituents, for example, basement membrane, collagen, and elastic-like tissues, of the cores of the trabeculae around the hole.

Discussion

In the last two decades various types of laser treatment of anterior chamber angle tissue have been performed in the hope of achieving a permanent improvement in outflow facility and therefore of reducing the intraocular pressure in primary open-angle glaucoma. The majority of the published work has concerned attempts to use the widely available argon ion laser, and since 1981 four papers²⁻⁵ have been published reporting remarkably consistent results from separate clinical trials of a new type of argon laser treatment following the protocol described by Wise *et al* in 1979.⁶

The long-term effectiveness of argon laser trabeculoplasty (ALT) has not yet been fully established, but in the short term reduced resistance to aqueous outflow seems to be due to the laser energy absorbed by the tissue acting thermally to shrink the meshwork at the site of each burn and so stretch the tissue between burns, opening up the intertrabecular spaces. This possible mechanism has not yet been fully investigated pathologically, but one SEM study of the effects of ALT⁷ has described fibrinous material and necrosis immediately after laser treatment, followed by a gradual occlusion of the intertrabecular spaces by migrating endothelial cells. A cellular reaction of this nature, combined with reactionary

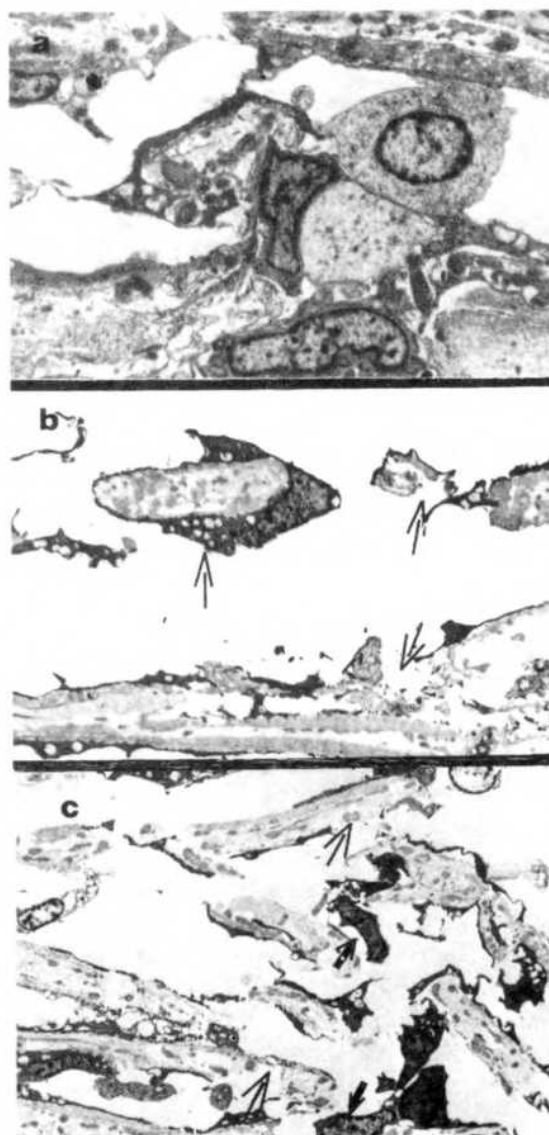


Fig. 5 Transmission electron micrographs of a laser hole made in fixed tissue by a single 31.2 mJ pulse at the HeNe focus (case 1): (a) the outer meshwork 200 μm from the edge of the hole—the morphology is within normal limits ($\times 3500$); (b) the uveal meshwork, 80 μm from the edge—the endothelial cells show cytoplasmic disruption ($\times 2000$); (c) The edge of the laser hole in the uveal meshwork—distorted and fragmented trabecular cores are in parts lined by disrupted endothelial cells (thin arrows) and occasionally by intact cells (thick arrows) ($\times 1640$).

fibrosis, could in theory cause a reduction of the outflow facility in the long term.

Q-switched laser pulses are quite different from

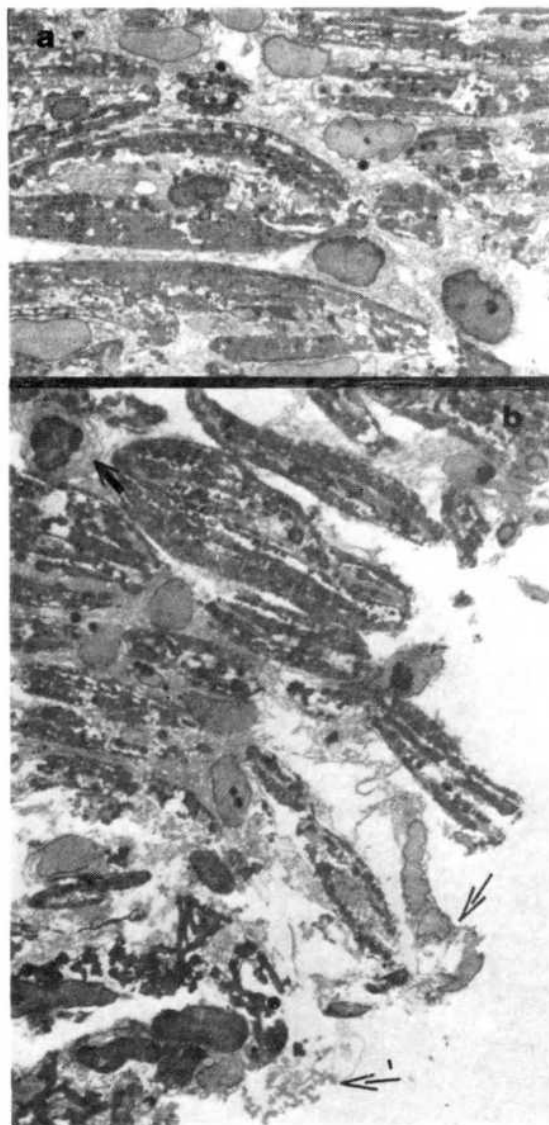


Fig. 6 Transmission electron micrographs of a laser hole made in unfixed tissue by a single 30.6 mJ pulse at 0.5 mm beyond the HeNe focus (case 5): (a) the outer meshwork 30 μ m from the edge of the hole shows autolytic cytoplasmic vacuolation only ($\times 2000$); (b) at the edge of the hole the trabeculae are fractured and the cells are ruptured (thin arrows); intact cells (thick arrow) are present within 30 μ m of the edge ($\times 2000$).

the output of continuous wave lasers in that they are several orders of magnitude greater in power, though low in energy. A typical neodymium/YAG laser, for example, could yield a Q-switched pulse of a few tens of millijoules but with a pulse duration so short that the power delivered during the pulse is one million

times that of a typical 0.1 s burst of argon laser radiation. Such high-power pulses, if sharply focused to give very high-power densities, cause damage by vapourising a very localised volume at their focus *without* raising the temperature of surrounding matter significantly. The destruction is caused by non-linear processes characteristic of very high electric fields rather than the more familiar chemical absorption, and so is largely independent of the colour of the target.⁸

These properties of Q-switched pulses—the localised non-thermal damage, and the ability to act on transparent tissue—make them an attractive choice for laser trabeculotomy. As long ago as 1972 Krasnov⁹ reported promising results using Q-switched pulses from a ruby laser to create large holes through meshwork into Schlemm's canal. Although it was effective in reducing the IOP in the short term, long-term follow-up showed a decline in the effectiveness of this technique in maintaining a reduced level of IOP, and it has not been generally adopted. Neodymium/YAG and neodymium/glass lasers have been used experimentally with some success, but clinical attempts to perform either laser trabeculotomies or cyclodialyses have been disappointing,¹⁰ possibly because of induced collapse of Schlemm's canal and closure of the laser opening respectively.

The in-vitro application of a well characterised and controlled YAG laser system to human tissue was considered to be essential for the study of the basic configurational features of laser induced trabeculotomies. The result of laser treatment in our experiments, as shown by light microscopy and scanning electron microscopy, was a series of tiny holes of roughly rounded cross section and generally extending into Schlemm's canal irrespective of the intrinsic thickness of the trabecular tissue. This suggests that the explosive force of the focused laser pulse was somewhat dissipated by the presence of the canal; it is interesting to note that any damage to the outer wall of the canal was well localised and superficial.

An interesting feature of our investigation is that no simple correlation was found between the dimensions of the laser-induced hole and the laser operating parameters within the chosen range. Various factors such as higher reflectivity made focusing more difficult for fresh tissue than for fixed, but in all cases there was considerable variability in the intrinsic architecture of the tissue, the extent of aging changes such as trabecular thickening and deposition of curly collagen, and the degree of autolysis before fixation. This variability may have masked any underlying pattern of dimensional dependence on pulse number or degree of defocusing.

It was not possible to approach the clinical in-vivo

situation in these experiments even with a freshly enucleated eye because of the degree of unavoidable autolysis that occurred while transporting the tissue to the laboratory and optimising the laser system's parameters just prior to use. We cannot really comment on any short- or long-term damage which a YAG system of this type might induce in endothelial cells around the site of a focused pulse in vivo. However, the results obtained from the TEM study of selected holes indicated that endothelial cells had an apparently undisturbed morphology outside a range of approximately 100 μm . In the best preserved fresh tissue (case 5) intact cells were found within 30 μm of the edge of the hole, and this raises the possibility that endothelial cell cover could be restored after in vivo laser treatment. Fragmentation of the trabecular cores was limited to a narrow band of approximately 20 to 30 μm from the edge of the hole, and it seems unlikely that, in vivo, liberated core materials would produce significant secondary obstruction to the canal. The most important problems still to be resolved in the use of the YAG laser to perform trabeculotomies are the subsequent repair response of the trabecular tissue and any unforeseen effects on other constituents of the anterior chamber in vivo. To our knowledge such information is not yet available, but preliminary primate experimental studies have yielded somewhat disappointing results.¹¹

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Risk of sudden visual loss following trabeculectomy in advanced primary open-angle glaucoma

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SUMMARY We studied the postoperative course of two groups of patients with primary open-angle glaucoma and small residual visual fields undergoing trabeculectomy. We found that there is a considerable risk of sudden loss of visual field after operation on these patients.

It is of concern to many ophthalmologists that patients with primary open-angle glaucoma and small residual visual fields may be at risk from sudden loss of that residual field as a result of drainage surgery. The evidence for such a fear is limited, and therefore a prospective study was undertaken specifically to evaluate the likelihood of acute visual loss following trabeculectomy for primary open-angle glaucoma.

Patients and methods

Twenty-six patients awaiting drainage surgery were included in this study. All had primary open-angle glaucoma diagnosed gonioscopically, with advanced cupping of the optic disc together with extensive visual field loss. Patients with other ocular pathology contributing to their visual loss were excluded from the study.

The patients were divided into two groups depending on the extent of their visual loss measured by Goldmann perimetry (which had been performed no more than six months preoperatively).

Group 1 ($n=9$) contained patients with visual field confined to a central island around 10° area $\pm$ a residual peripheral island (Fig. 1). Group 2 ($n=17$) contained patients with visual field loss encroaching into the central 10° meridian with part of the residual field lying outside this area (Fig. 2).

All the patients underwent trabeculectomy by various surgeons. Any intra- or postoperative complications were recorded. Ten to 12 weeks after operation, when the eyes were free from inflammation and all local steroids and mydriatics had been discontinued, tests of visual acuity and Goldmann perimetry were performed. The level of intraocular

pressure control was recorded and a note made of any new ocular pathology contributing to any of the changes observed.

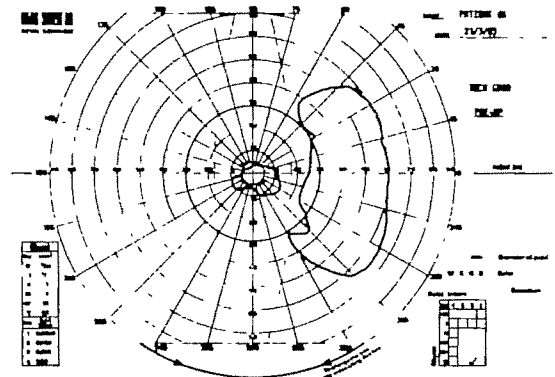


Fig. 1 Example of patients in group 1 (patient 6a).

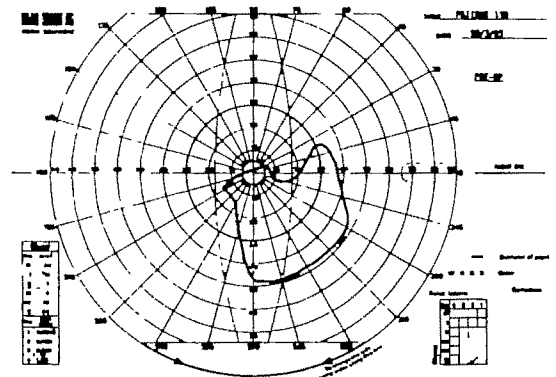


Fig. 2 Example of patients in group 2 (patient 11b).

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Results

GROUP 1

Nine patients were included in this group with ages ranging from 60 to 83 years (mean 71). Six of the patients were unchanged in their postoperative measurements of visual acuity and visual fields. Three of the nine (33%) experienced loss of their central visual field with a concomitant reduction of their central visual acuity (Table 1). All the patients had good postoperative control of intraocular pressure, none requiring any additional medication on follow-up ranging from seven to 24 months. Patient 1a had a partly torn scleral flap at the time of surgery. Postoperatively she developed cystoid macular oedema, confirmed clinically by slit-lamp examination with a fundus contact lens. This resolved, leaving residual scarring at the macula.

Patient 7a had a moderately shallow postoperative anterior chamber for three days followed by complete resolution.

Patient 9a had an unremarkable intra- and post-operative course. None of the patients were at any time noted to have a raised intraocular pressure after operation.

GROUP 2

This group comprised 17 patients ranging in age from 45 to 82 (mean 66). Six had postoperative visual field changes (35%) (Table 2). Although five of the

patients (29%) showed a reduction in their visual fields, only one (9b) lost the central field, with consequent drop in visual acuity. One of the patients showed some improvement in the peripheral visual field probably attributable to discontinuing the miotics (10b).

Discussion

Since the introduction of surgery for glaucoma, ophthalmologists have pondered the risks of central visual loss after filtering operations. Several authors have stressed the dangers of performing surgery in patients with advanced glaucomatous field loss^{1,2} and cautioned against such procedures, while others have suggested that the dangers, if any, are minimal.^{3,4}

Our results show that in patients with a very small field (<10°) and primary open-angle glaucoma there does exist a definite risk of central visual field loss (group 1). Of the three patients in this group who showed such changes one had cystoid macular oedema. Indeed some authors⁵ have thought that this accounts for such changes. One of the remaining two patients had a moderately shallow anterior chamber post operatively, persisting for several days. Perhaps, as has been suggested, this persistent hypotony may have been responsible for the central visual loss.^{1,2} The third patient had no identifiable cause of this visual loss.

In our second group only one patient showed central visual changes, though five of the patients in this group did show a reduction of their visual fields. All these patients had an uneventful operative and postoperative course.

We consider that, whatever the reasons for the changes observed in these patients, there does appear to be a definite risk of sudden deterioration of central vision in patients with advanced primary open-angle glaucoma and severe visual field loss. Hence special caution should be exercised before performing filtering procedures on them.

Table 1 Group 1 patients: details of patients showing postoperative central visual loss

Patient no	Age	Preoperative		Postoperative		Follow-up (months)
		VA	IOP	VA	IOP	
1a	60	6/12	26	6/36	14	9
7a	69	6/12	26	HM	10	7
9a	67	6/6	22	6/36	16	24

Table 2 Group 2 patients: visual field changes in patients in group 2

Patient no.	Age	Preoperative		Postoperative		Visual field changes	Follow-up (months)
		VA	IOP	VA	IOP		
6b	69	6/6—	29	6/9+	16	Constriction of peripheral field	10
9b	78	6/18	29	6/36	14	Field reduced to small central island with separate peripheral island	26
10b	66	6/6	32	6/9	16	Field improved peripherally	8
11b	77	6/9	24	6/9	9	Reduced to small central island with separate peripheral island	6
12b	77	6/18+	32	6/18+	12	Peripheral field constriction	•
17b	78	6/12	21	6/12	12	Reduced to small central field	6

These operations should perhaps be reserved for patients whose condition is inadequately controlled on medical therapy and shows certain evidence of progression. The present tendency towards early surgery in the management of glaucoma makes this all the more necessary in these groups of patients.

We thank the consultants of Coventry and Warwickshire and East Birmingham Hospitals for allowing us to study their patients and their respective orthoptic departments for performing the tests of visual fields. We also thank Mr H E Wilshaw and Mrs M C Handscombe for their help in the preparation of this paper. Mrs C

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Choroidal metastasis of adenocystic carcinoma of the salivary gland

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SUMMARY A case of adenocystic carcinoma of the salivary gland arising in the hard palate metastatic to the choroid is presented. The histopathology of the tumour is discussed.

Metastatic tumour is the most common intraocular neoplasm.¹ The list of primary tumours which metastasise to the choroid is legion. It is surprising that there has never been a previous histopathological report of an adenocystic carcinoma of the salivary gland metastatic to choroid.

Case history

An 88-year-old widowed cabinet-maker presented to his ophthalmologist complaining of difficulty driving because of constant blurred vision of the right eye for one week. He had had transurethral resection of the prostate 12 years previously for benign prostatic hypertrophy. One year ago a lump in the hard palate was noted. An excisional biopsy was attempted, and the specimen revealed adenocystic carcinoma of the salivary gland, incompletely excised. A bone scan at that time had been negative. No further treatment was undertaken.

Eye examination showed best corrected visual acuity of 6/200 OD and 6/7 OS. The right eye had a heavy episcleral complex of vessels. The anterior segment OS was unremarkable. Applanation tensions were 22 mmHg OD and 19 mmHg OS. Funduscopy showed peripapillary atrophy OU. An inferior retinal detachment was seen OD, with the suggestion of an underlying mass.

The right eye was enucleated for presumed choroidal melanoma and sent to the David G Cogan Eye Pathology Laboratory at the Massachusetts Eye and Ear Infirmary for histopathological examination. A preoperative chest X-ray was reported as normal. A subsequent bone scan showed increased activity

only in the hard palate and at sites of degenerative joint disease. A liver-spleen scan showed questionable low activity in the left lobe and hilum of the liver without hepatomegaly. This was thought to be suspicious for metastasis.

DESCRIPTION OF SPECIMEN

The globe fixed in formalin measured 20×22×22 mm. External examination revealed no extrascleral tumour. A transillumination defect was noted inferotemporally. The anterior, posterior, and vitreous chambers were filled with a whitish material. A tumour 16 mm in its greatest diameter and 2 mm in elevation was noted beneath the retina, apparently contiguous with the choroid (Fig. 1a).

Microscopically the tumour showed nests of densely packed cells with large, lacy nuclei and scant cytoplasm (Fig. 1b). Hyaline bands surrounded the nests. Many nuclei showed prominent nucleoli, and from four to 12 mitotic figures per high-power field were visible. The tumour appeared poorly differentiated. Superficial invasion of the scleral coat was seen. Alcian blue stains revealed the presence of intercellular acid mucopolysaccharide. The retina was detached and appeared necrotic directly underlying the tumour. Subretinal fluid was evident. The anterior, posterior, and vitreous chambers contained amorphous eosinophilic material. The remaining intraocular structures were unremarkable for the globe of an 88-year-old patient.

The tissue from the hard-palate tumour was obtained and reviewed. It was found to contain similar nests of cells with lacy nuclei and scant cytoplasm surrounded by hyaline bands (Figs. 2a and 2b). Areas of well differentiated tumour and areas of more poorly differentiated tumour were identified, the latter areas resembling the intraocular tumour.

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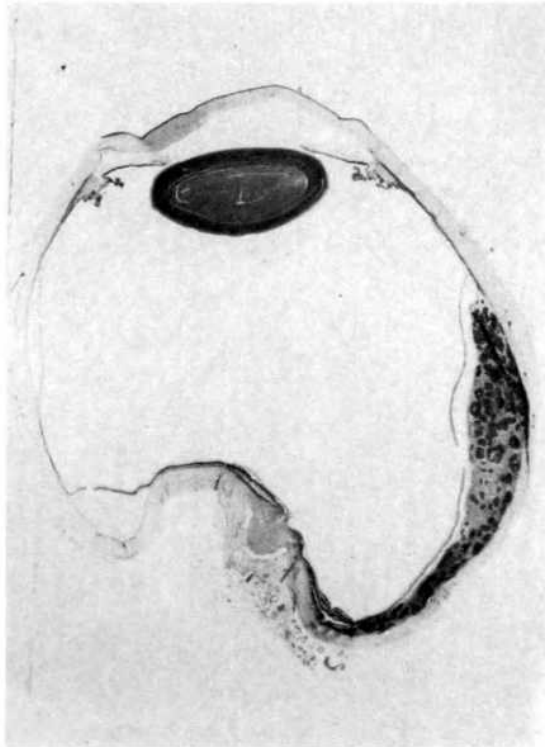


Fig. 1a Vertical section through the globe demonstrating metastatic adenocystic carcinoma of the salivary gland in the choroid. (H and E, $\times 2.8$).

Discussion

Metastatic tumours are the commonest intraocular neoplasm, a fact previously obscured by the typically late development of ocular metastasis in the moribund patient with carcinoma and the infrequency of examination of ocular tissue in routine necropsy of cancer patients.¹ The incidence of ocular metastasis in patients with known malignancies has been variably reported by several authors. Godtfredsen reported ocular metastasis in six cases out of 8712 patients with known carcinoma.²

Albert, Rubenstein, and Scheie found 10 cases of clinically debatable metastasis to the eye and orbit in 213 patients with known non-ocular metastatic disease. Five of these cases had metastasis to the choroid.³ Bloch and Gartner reported 28 histopathologically demonstrated foci of metastasis to the eye and orbit from an examination of 230 patients who had died of systemic cancer. The incidence of intraocular metastasis in these cases was 11%.⁴

By far the most frequent primary cancers to metastasise to the eye are from the breast and lung, representing 39% and 17% of metastases in the Massachusetts Eye and Ear Infirmary series 1896–1981.¹ Other primary neoplasms in this series responsible for ocular metastasis include neuroblastoma, skin melanoma, kidney, liver, testis and urogenital ridge, pancreas, prostate, intestine, stomach, aesthesioneuroblastoma, myxoma, carcinoid, and hypophyseal tumour.

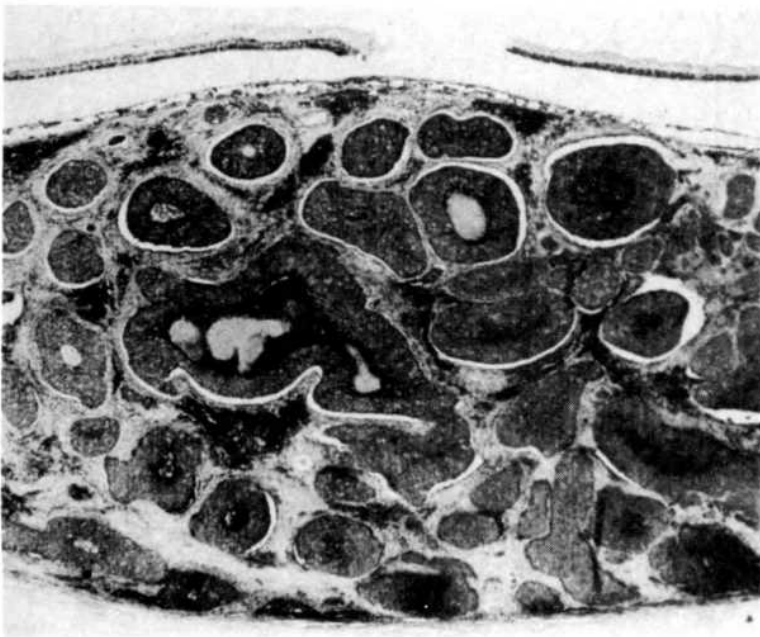


Fig. 1b Nests of poorly differentiated cells surrounded by hyaline bands underlying the retina. (H and E, $\times 13$).

Fig.2a Pattern of nests of cells surrounded by hyaline bands in hard palate tumour resembling nests in choroidal tumour. (H and E, $\times 144$).

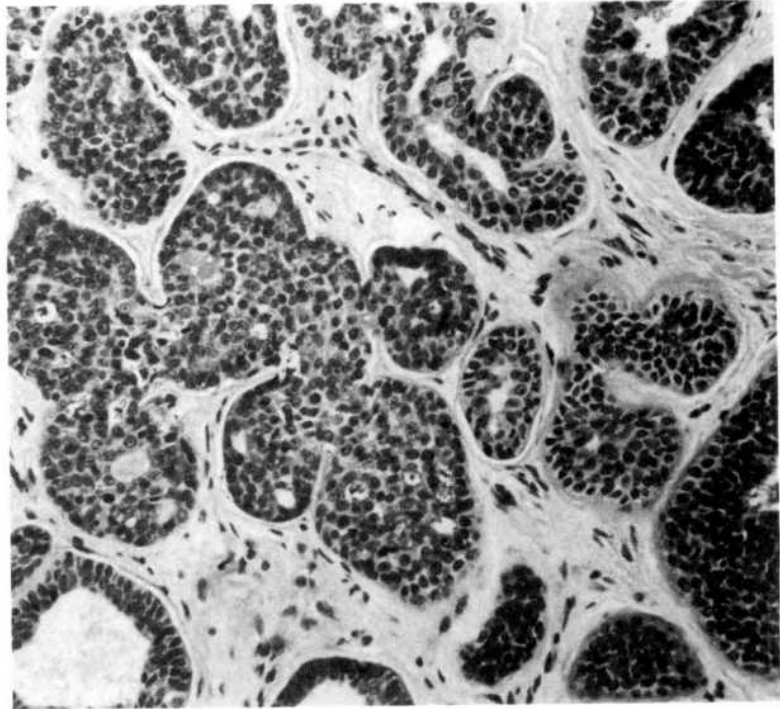
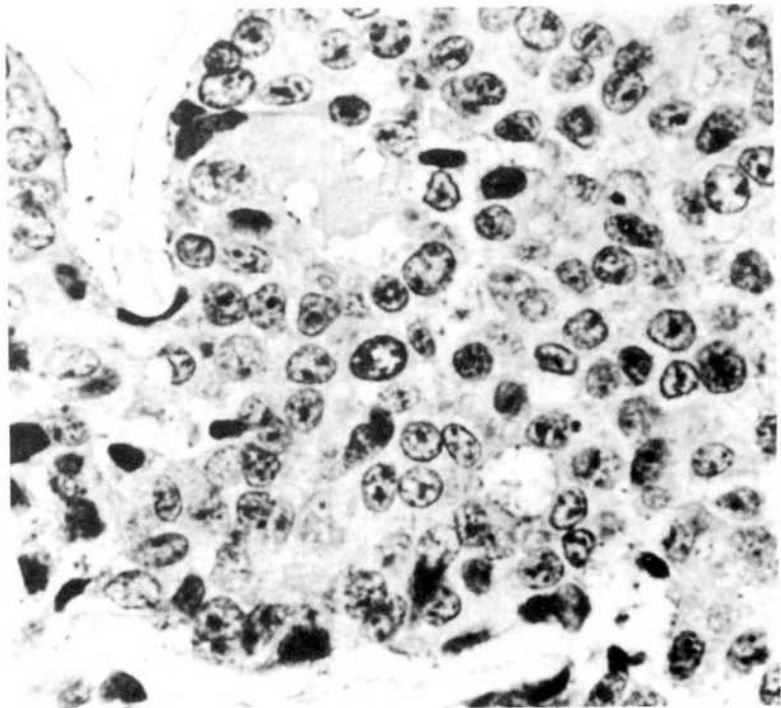


Fig.2b High-power view of an area of relatively well differentiated palate tumour demonstrating lacy nuclei with prominent nucleoli and frequent mitoses. (H and E, $\times 576$).



In 227 cases of carcinoma metastatic to the eyes and orbit reviewed by Ferry and Font the presenting complaint was decreased vision in 79.9%, pain in 22.4%, and retinal detachment in 11.4%.³

Many lesions may mimic melanoma of the choroid. In the Wills series of 770 patients referred because of ophthalmoscopically suspected melanoma 52% were diagnosed as having various simulating lesions.⁴

Histological examination of ocular metastatic adenocarcinoma of the salivary gland has to our knowledge not been previously reported. Sautter described a case of presumed bilateral metastasis to the choroid in patients with adenocarcinoma of a minor salivary gland invading the mandible.⁷ The eyes were not examined post mortem. Jenrette and Fitzgerald described a case of presumed choroidal metastasis two months after complete response to systemic chemotherapy for adenocystic carcinoma of the salivary gland with disappearance of pulmonary metastasis.⁸ The choroidal lesions completely disappeared with local radiation therapy; consequently no histopathological examination was available.

While enucleation may be curative for primary malignant melanoma arising in the choroid, palliative radiation therapy is generally the preferred course for metastatic disease of the choroid. In only one published case, that of a carcinoid tumour metastatic to the eye 30 months after excision of the primary, has enucleation of a metastatic cancer been curative.⁹ Every effort should therefore be made to diagnose metastasis prior to definitive enucleation.

Clues in this critical differential diagnosis may be gained by a careful clinical history with reference to general systemic symptoms and past medical history. A thorough general physical examination should be undertaken. A search for metastases including chest X-ray, liver function tests, liver-spleen scan, and bone scan, would not only expose the most likely sites for metastatic choroidal melanoma, but also disclose the most likely sites for a primary cancer metastatic to the choroid.

The characteristics of the growth pattern of a melanoma may serve to differentiate it from metastases which may be flatter, multifocal, or bilateral. Fluorescein angiography may provide helpful information. Ultrasonography of the eye may be useful. B-mode scanning may be of use to define characteristic tumour morphology and choroidal excavation; a-mode scanning may show characteristic acoustic patterns of melanoma or of metastasis.

This case describes the (previously unreported) histopathological demonstration of a choroidal metastasis from a primary adenocystic carcinoma of the salivary gland arising in the hard palate and stresses the need to formulate a preoperative differential diagnosis between primary melanoma of the choroid and metastatic choroidal disease.

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Focal fluorescence of choroidal melanoma*

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SUMMARY The surface of the tumours of four patients with apparently dormant small choroidal melanomas showed a distinct, localised, hyperfluorescent zone by fluorescein angiography. It was interpreted as being secondary to atrophy of the retinal pigment epithelium. In each patient later growth of the tumour was evidenced by its eruption through Bruch's membrane at this same site. This angiographic finding may predict a tumour that is prone to grow and break through Bruch's membrane at that location.

Many patients with a small choroidal melanoma are managed by a period of observation for recording of the tumour's growth before treatment is recommended.^{1,2} We have recently recognised an unusual fluorescein angiographic pattern that preceded clinically evident eruption of several melanomas through Bruch's membrane.

Case reports

CASE 1

A 65-year-old man presented to the Oncology Service in January 1984. He had previously undergone intracapsular cataract extractions with implantation of an anterior chamber intraocular lens in both eyes. Over the previous several months he had noted blurred vision in the right eye. Examination revealed visual acuity of 20/80 in the right eye and 20/20 in the left. Ophthalmoscopy of the right eye showed a small amelanotic choroidal melanoma in the inferior macula estimated to be 5.5 × 5 mm in basal diameter (Fig. 1). Ultrasonography showed its thickness to be 3 mm. Fluorescein angiography showed early mottled hyperfluorescence over the entire tumour with a distinct localised hyperfluorescent site just nasal to the centre, which was consistent with an area of retinal pigment epithelial attenuation (Fig. 2). Owing to the tumour's small size and proximity to the disc and macula, we decided to observe the tumour for growth before considering treatment.

Follow-up examination three months later revealed a nodular eruption through Bruch's membrane at the previously hyperfluorescent focus (Fig. 3). A moderate amount of subretinal fluid and haemorrhage was also noted. The patient was treated by iridium-192 plaque therapy.

CASE 2

In May 1984 a 45-year-old man was found to have a small amelanotic choroidal melanoma just nasal to the optic disc in his right eye (Fig. 4). The tumour was approximately 10 × 6 × 3.5 mm in size. Fluorescein angiography showed mottled early hyperfluorescence, with a focal area on the temporal aspect of the tumour that showed earlier, more pronounced

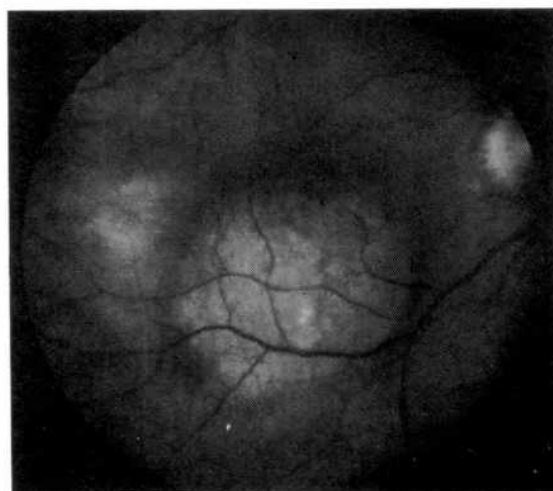


Fig. 1 Fundus photograph of choroidal melanoma (case 1).

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*Presented in part at the Wills Eye Hospital Annual Fluorescein Angiography Conference, 7 September 1984.

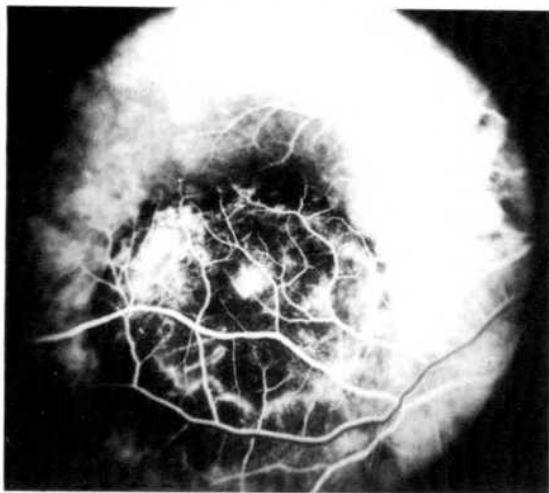


Fig. 2 Fluorescein angiogram of tumour seen in Fig. 1. Note the conspicuous area of increased hyperfluorescence.

hyperfluorescence (Fig. 5). A decision was made to observe the tumour for growth before treatment.

In September 1984 the patient returned for scheduled follow-up. A large nodular eruption through Bruch's membrane was noted at the site of the previously noted transmission defect (Fig. 6). The patient was treated then by radioactive iridium plaque therapy.

CASE 3

In September 1982 a 62-year-old patient with glaucoma presented with a one-year history of blurred vision in the right eye. Examination revealed visual acuity of 20/200 and 20/20 in the right and left eyes respectively. Ocular examination revealed a

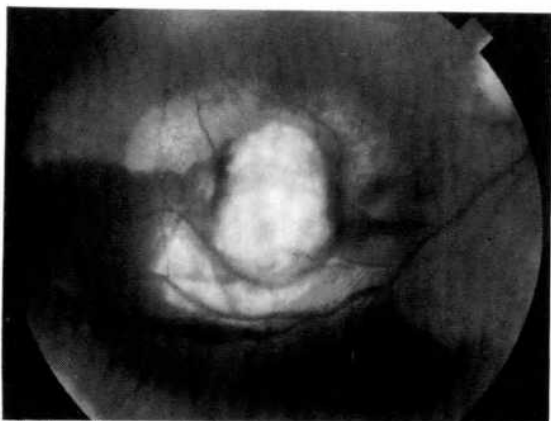


Fig. 3 Follow-up fundus photograph showing tumour breaking through Bruch's membrane at the site of previous hyperfluorescence.

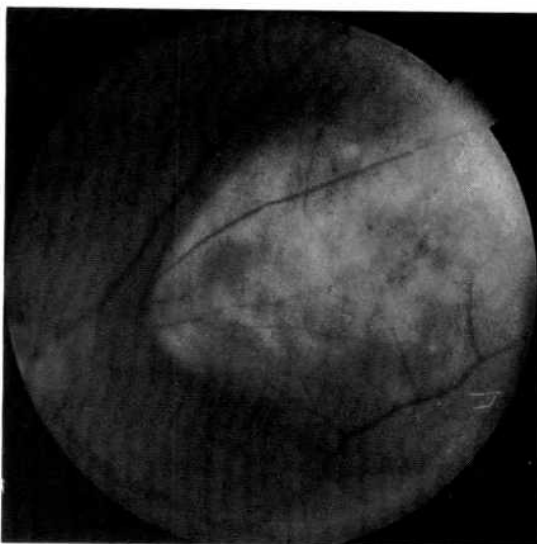


Fig. 4 Fundus of case 2. Note the small tumour nasal to the optic disc.

small choroidal tumour measuring $3.5 \times 3 \times 1.5$ mm in size in the foveal region of the right eye. Fluorescein angiography showed early hypofluorescence except for a small isolated hyperfluorescent transmission defect. Late-phase frames showed diffuse mottled hyperfluorescence of the tumour.

Periodic follow-up examinations showed no appreciable change in this tumour until July 1984, when the patient returned with a visual acuity in the right eye reduced to counting fingers. Examination

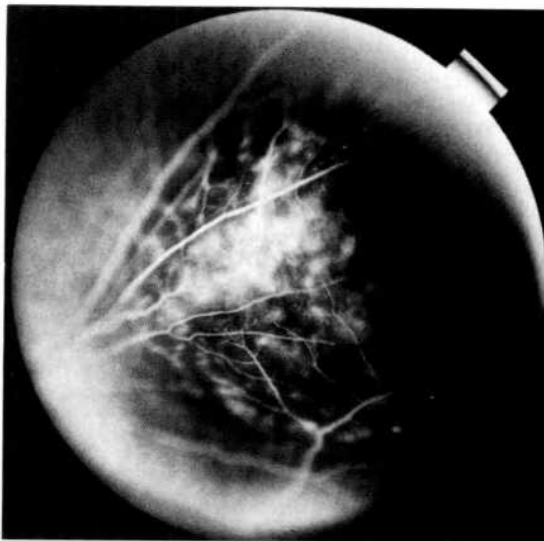


Fig. 5 Fluorescein angiogram of tumour seen in Fig. 4. An area of increased hyperfluorescence is present.

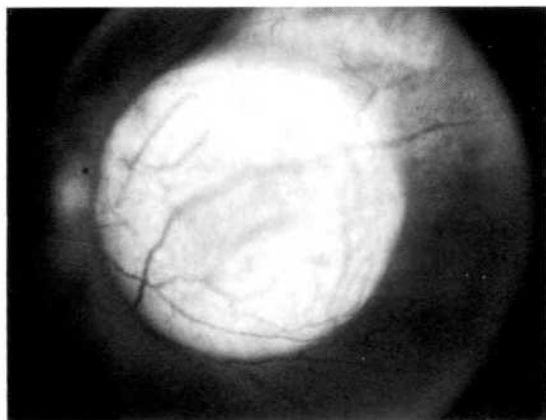


Fig. 6 Follow-up fundus photograph of case 2. Note the large tumour eruption through Bruch's membrane.

showed that the tumour had broken through Bruch's membrane at the site of the previous window defect. An enucleation was performed. Pathological examination identified the tumour as a spindle-B cell melanoma and confirmed the eruption through Bruch's membrane (Fig. 7).

CASE 4

A 35-year-old man was referred to the Oncology Service for evaluation of a choroidal lesion. In December 1981 examination revealed normal vision in both eyes. Ophthalmoscopy showed an amelanotic choroidal melanoma measuring approximately $6 \times 4 \times 2.5$ mm and located 3 mm nasal to the optic disc in the right eye. Fluorescein angiography showed a small focus of hyperfluorescence in the early-phase frames.

The patient returned in November 1984 with a definite eruption of the tumour through Bruch's membrane at the site of the previously noted transmission defect. The tumour was treated by radioactive iridium plaque therapy.

Discussion

These four cases are similar in several ways. They are all examples of small choroidal melanomas near the optic disc or fovea that were observed for growth before proceeding with treatment. All four tumours developed a well-defined focus of early intense hyperfluorescence on the initial angiogram consistent with localised attenuation of the retinal pigment epithelium. These sites were not evident by comprehensive ophthalmoscopic examination. Subsequent examinations revealed that all these tumours had enlarged, with eruption of the tumour through Bruch's membrane in the area of the angiographic transmission defect.

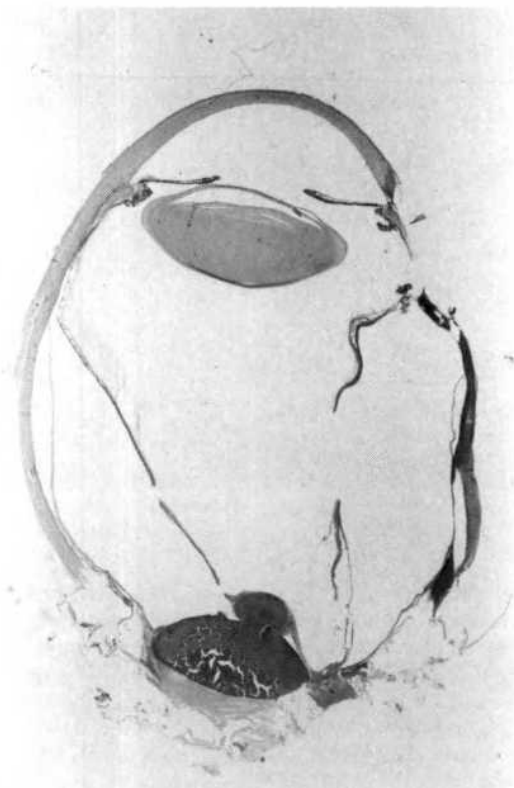


Fig. 7 Microscopic examination of tumour in case 3. Note eruption through Bruch's membrane and mushroom configuration. (Haematoxyl-eosin, $\times 0.6$).

On the basis of this series of cases we suggest that the finding of focal intense hyperfluorescence on the surface of a small choroidal melanoma predicts that the tumour is active and that it will enlarge by erupting through Bruch's membrane at that site. We believe that this angiographic finding should be included in the group of other clinical signs that identify those small choroidal melanomas that are prone to grow.¹² If the fluorescein angiograms of other patients with small melanomas which eventually erupt through Bruch's membrane are studied carefully, other cases of this type may be recognised.

We thank Drs David Harris, George Kranias, George Spaeth, and Arnold Traupman for kindly referring the above patients.

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Malignant melanoma of the choroid in a mother and retinoblastoma in her son

SEIJI HAYASAKA AND KATSUYOSHI MIZUNO

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SUMMARY A 31-year-old woman was diagnosed as having a malignant melanoma of the choroid in the right eye. Twenty months later her 7-year-old son was diagnosed as having retinoblastoma in the right eye. Both diagnoses were confirmed histopathologically after enucleation. A chromosomal study revealed normal karyotypes in the son. The family history was positive for cancer of the stomach. The implications of this rare association are discussed.

Cancers have been noted to occur with high frequency among blood relatives.^{1,2} The hereditary aspects of retinoblastoma in particular have been reported in relatives of affected children.^{3,4} Retinoblastoma is rarely found in patients after the age of 7,^{5,6} and uveal malignant melanoma is also uncommon in the Japanese population.⁷ We describe a rare malignant melanoma of the choroid in a mother and retinoblastoma in her 7-year-old son in a pedigree with a hereditary tendency to stomach cancer.

Family and case reports

The family tree (Fig. 1) shows a hereditary tendency to stomach cancer in this pedigree: cases I-4, I-6, II-1,

II-6, II-13, and III-2 died of stomach cancer. Case II-5 died of oesophageal cancer. Case III-3 died of carcinoma of the corporis uteri. Cases I-1, I-2, I-5, and II-4 possibly died from cerebral apoplexy. Case I-3 died of puerperal fever. Cases II-2, II-3, II-7, and III-1 died early in life, but their medical records were not available. Case II-12 was under examination for possible stomach cancer.

CASE III-14 (PROBAND)

A 31-year-old woman noticed blurred vision in her right eye on 30 December 1982. The next day she was referred to Tohoku University Hospital. Her past medical history was non-contributory. Her best corrected vision was 0.6 OD and 1.2 OS. The intraocular pressure was 12 mmHg OU. The eye positions and movements were normal. The cornea, anterior chamber, and lens were transparent bilaterally. Her irides were brown, with no heterochromia. Ophthalmoscopically a tumour 7 disc diameters long

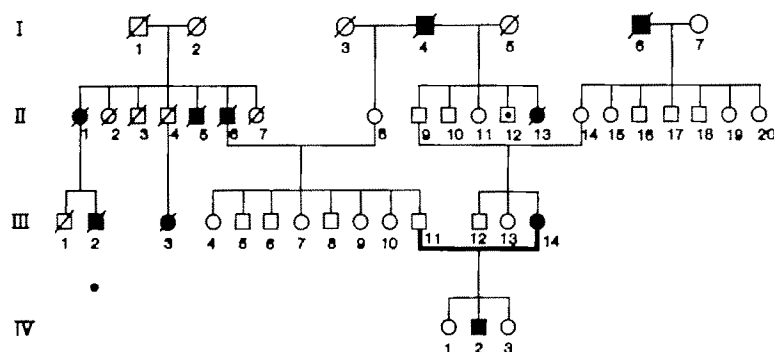


Fig 1 The family tree □ male; ○ female; ■ male with malignant neoplasm; ● female with malignant neoplasm, ◻ male suspected of malignant neoplasm, /=died; ==consanguineous marriage

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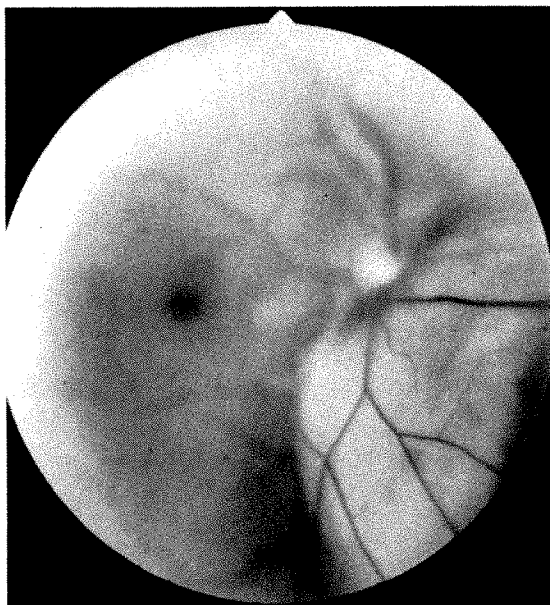


Fig. 2 Fundus photograph of the proband (case III-14). Pigmented tumorous mass is visible inferonasally in the right fundus.

and 5 dioptries deep was found inferonasally in the right eye. Spotted pigmentation was noted under the surface of mass (Fig. 2). The clinical impression of malignant melanoma was supported by fluorescein angiography, orbital computed tomography, and ultrasonography. Systemic examination and laboratory studies were negative for extraocular melanoma.



Fig. 3a Histopathological specimen from the right eye of the proband. Pigmented mass is visible near the optic disc. (H and E, $\times 3$).

Late in January a secondary retinal detachment extended to the macular area, and visual acuity in the right eye decreased to 0.05. On 1 February 1983 the right eye was enucleated. Pathological examination showed a malignant melanoma of the choroid, predominantly composed of spindle B cells, without scleral or extraocular invasion (Figs. 3a, b). In March 1985 the patient was alive and well with no evidence of metastatic disease.

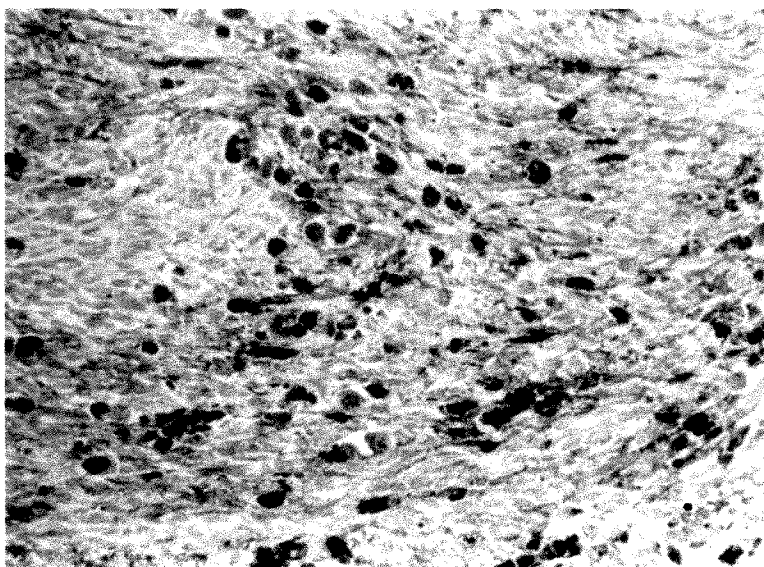


Fig. 3b Histopathological specimen from the right eye of the proband. High magnification shows spindle B melanoma cells. (H and E, $\times 150$).

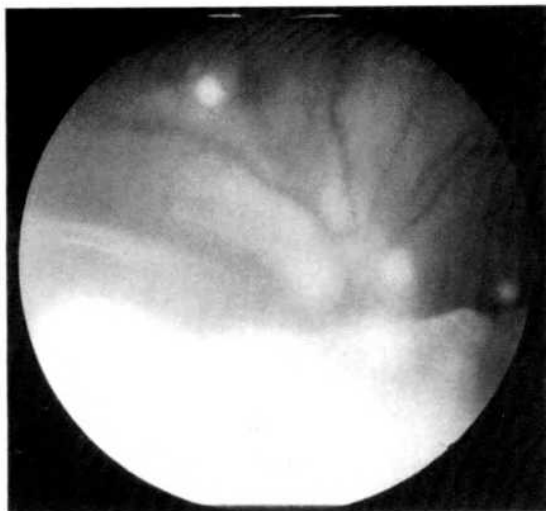


Fig. 4 Fundus photograph of the proband's son (case IV-2) shows a yellowish-white mass, retinal detachment, and floating clusters.

CASE IV-2 (SON OF PROBAND)

The boy's parents were consanguineous. Because of his mother's condition the child was examined by indirect ophthalmoscopy in January 1983 at the age of 6 years. His fundi appeared normal. On 22 March 1984 his right eye was struck with a pencil at school. His corrected vision was 1.0 OU. A slit-lamp examination disclosed a small conjunctival laceration, which healed two weeks later. An ophthalmoscopic examination showed no haemorrhage, oedema, or tumour in the right fundus.

On 1 September 1984, at the age of 7, he returned to us with a white pupil. His visual acuity was hand motions OD and 1.0 with myopic correction (-0.25 D) OS. The intraocular pressure was 12 mmHg OD and 15 mmHg OS. The cornea, anterior chamber, and lens were clear bilaterally. Ophthalmoscopically a yellowish-white mass 6 disc diameters in length and 4 dioptres in depth and a retinal detachment were seen inferiorly in the right eye (Fig. 4). Neovascularisation was noted under the surface of the mass, but pigmentation was not found. Several small whitish clusters floated in the posterior vitreous. A single bright-flash ERG response was subnormal in the right eye and normal in the left. The clinical impression of retinoblastoma was supported by ultrasonography and orbital computed tomography. Systemic evaluation and laboratory studies were negative for extraocular extension. A chromosomal analysis revealed normal karyotypes. On 11 September 1984 the involved right eye was enucleated. An increased level of lactic dehydro-

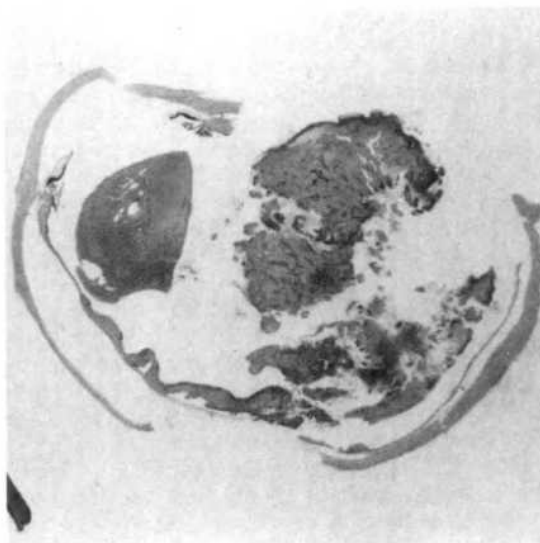


Fig. 5a

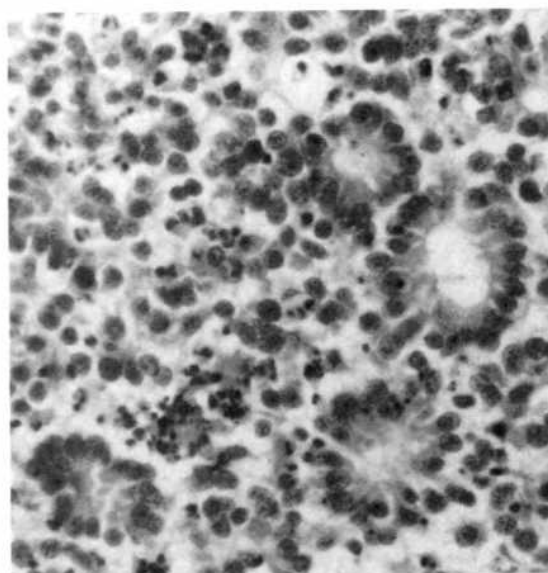


Fig. 5b

Fig. 5 Histopathological specimen from the right eye of the proband's son. (a) Tumorous mass extends into the vitreous cavity. (H and E, $\times 3$). (b) Flexner-Wintersteiner rosettes are visible. (H and E, $\times 250$).

genase activity was found in the aqueous humour. Pathological examination showed a retinoblastoma composed of rosette formations without extraocular extension of the tumour (Figs. 5a, b). In March 1985 the patient was alive and well with no evidence of metastatic disease.

Discussion

An unusual association of uveal malignant melanoma in a mother and retinoblastoma in her son was observed. A hereditary tendency for cancer of the stomach was noted in the family. Consanguineous marriage was also found. It is unknown whether the familial occurrence of stomach cancer or parental consanguinity was related to the pathogenesis of the ocular malignancy, despite the positive family history.⁴

The incidence of uveal malignant melanoma varies markedly among different races.⁸ Ocular malignant melanoma, such as that found in our proband, is very rare in Japan.⁷ Only a few cases of uveal malignant melanoma have developed in blood relatives⁹ and in spouses.¹⁰ However, the importance of hereditary or familial factors in the aetiology of uveal malignant melanoma in humans is still obscure.

Retinoblastoma can be hereditary or non-hereditary. The hereditary form is found in all cases of bilateral retinoblastoma and in a small group of unilateral cases.¹¹ Chromosome 13 deletion has been reported in some patients with familial retinoblastoma.¹² Our case IV-2 (son) had unilateral retinoblastoma and normal chromosomal findings, suggesting a non-hereditary form of the disease. His intraocular tumor was discovered at the age of 7 years. Five months before this his fundi appeared normal ophthalmoscopically, pointing to the rapid growth of the retinoblastoma.

Death due to melanoma in two relatives of patients with bilateral retinoblastoma has been reported in one family.³ However, we have no apparent explanation for the rare occurrence of the two different neoplasms in our family. Electron microscopy failed

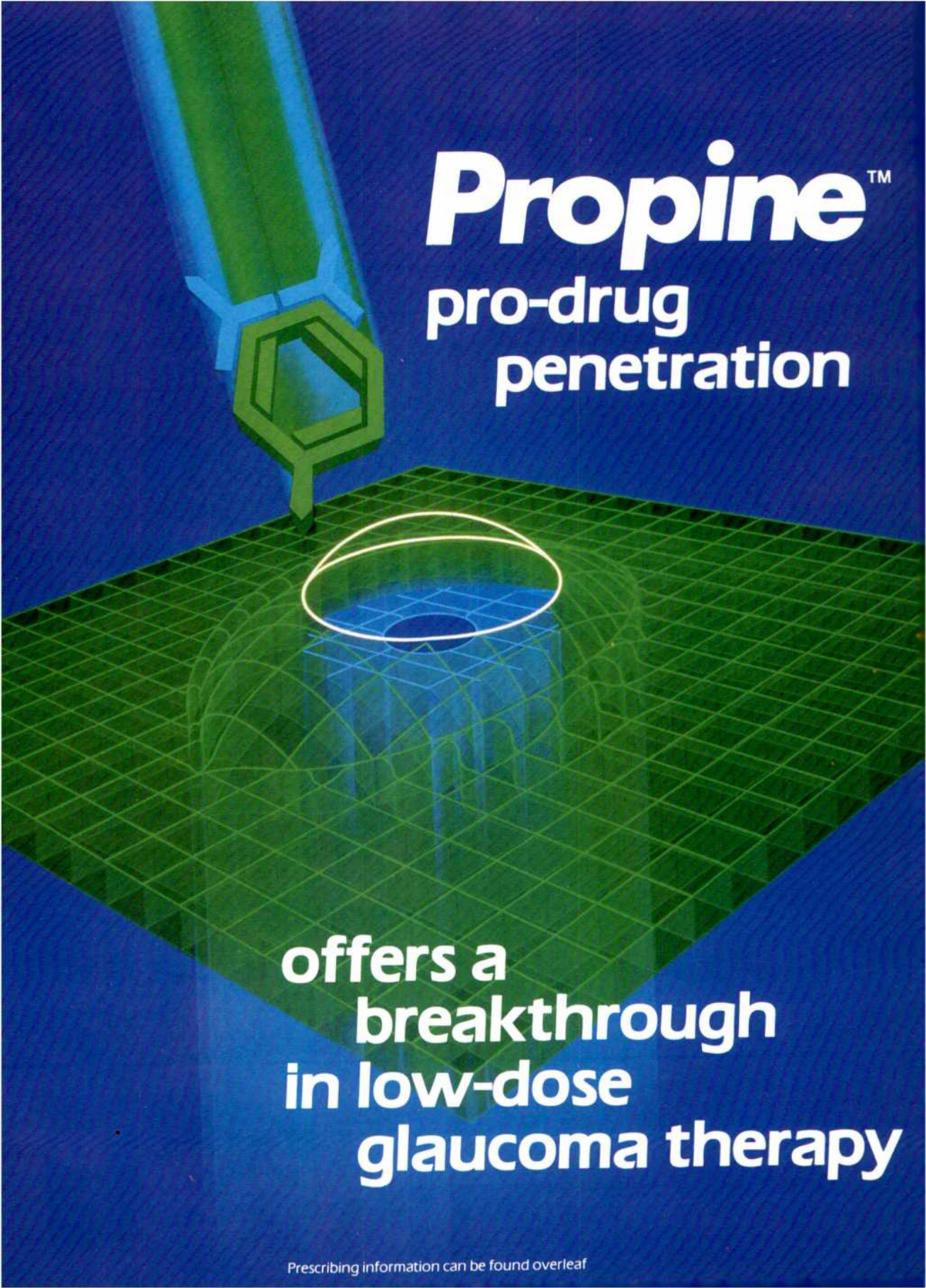
to reveal viral particles in the tumours in our cases, and chromosomal analysis showed normal findings. Perhaps other such cases reported in future may reveal common aetiological factors.

The authors thank Dr T Yamada for preparing the figures, and Ms M Gere for editing the manuscript.

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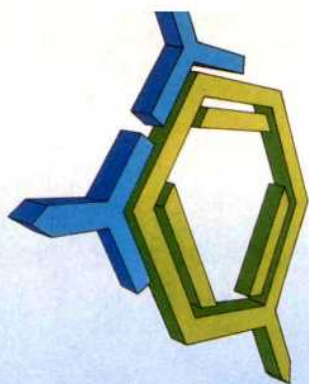


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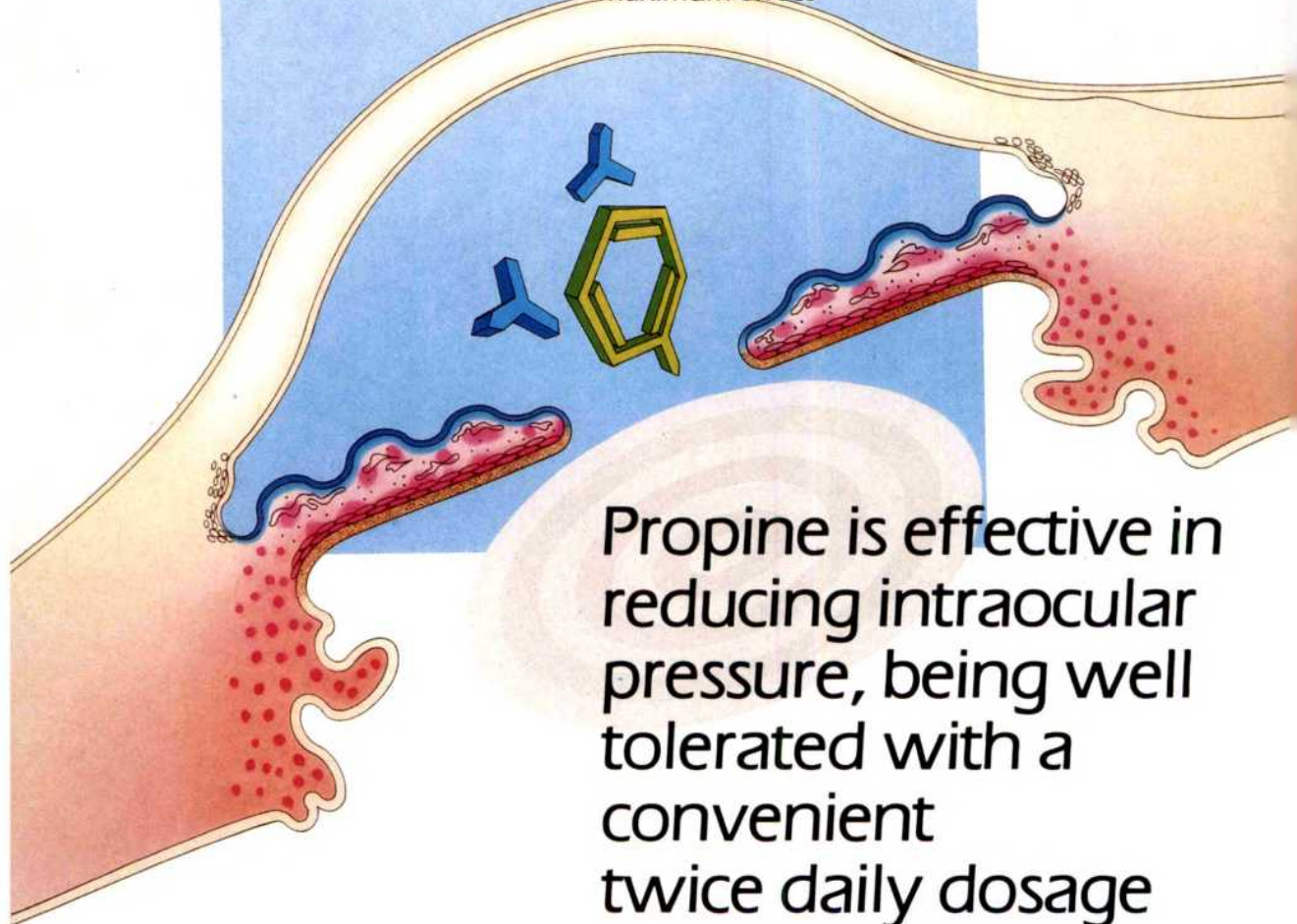
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Congenital orbital-intracranial teratoma with subsequent malignancy: case report

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SUMMARY A newborn baby had an orbital-intracranial benign teratoma radically excised with preservation of the eye. Three years later she developed recurrent proptosis, and reoperation showed an invasive orbital tumour that histologically was a malignant germ-cell neoplasm. The relationship of the two tumours is discussed. Malignant change in a benign orbital-intracranial teratoma of the newborn has not been previously reported.

The following report, that of an infant girl who underwent excision of an orbital-intracranial teratoma with recurrence as a malignant tumour at age 3 years is of interest.

Case report

The patient was seen at age 2 days for a proptosis of the right eye. On examination she failed to fixate a hand light with either eye, and there was no optico-kinetic response. Exophthalmometry readings were 15 mm right and 10 mm left (Luedde). Extraocular motility was full. Palpably the eyes were symmetrically firm and could not be ballotted. No bruits could be heard. Fundusoscopic examination revealed a normal sized vasculature, sharp discs, and scattered blot haemorrhages in both eyes. The results of laboratory tests for routine haematological and biochemical values were within normal limits. A CT scan showed a large, inhomogeneous mass in the right orbit extending into the nasopharynx, the maxillary sinus, and the anterior cranial fossa.

Surgically the tumour was approached via a bifrontal craniotomy, orbitotomy, and lateral rhinotomy, with apparent total removal. Pathologically the orbital tumour was a 2×1.25 cm cystic nodule which microscopically had smooth muscle forming the wall and a lining of columnar epithelium (Fig. 1A). The anterior fossa portion of the tumour was a 4 cm mass with neuroglial and fibrofatty tissue (Fig. 1B). A 2.5 cm cystic nodule lined by squamous epithelium with skin appendages and cartilage in the

wall formed the nasal portion (Fig. 1C). All three germinal layers were represented and no malignant elements were identified. Four months after surgery the patient followed lights and objects equally well, the corneal light reflexes were symmetrical, and her exophthalmometry reading was 14 mm in both eyes (Hertel). Both pupillary reactions were brisk, and the fundus haemorrhages had cleared.

The patient was well until age 3, when she was noted to have swollen lids and chemosis on the right. Subsequently she did not fixate objects with the right eye, the right eye became proptotic, and a right Marcus Gunn pupil was noted. Exophthalmometry readings were 26 mm right eye and 14 mm left eye (Hertel). The right eye was displaced inferonasally,

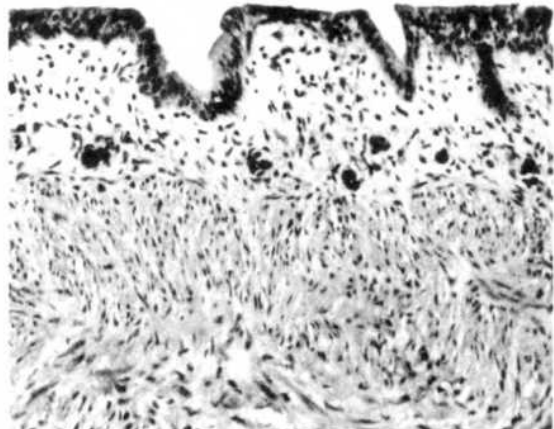


Fig. 1A Cyst wall showing smooth muscle and lining of columnar epithelium. (Haematoxylin and eosin, ×100).

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Fig. 1B Portion of tumour with glial tissue and neurons. (Haematoxylin and eosin, $\times 100$).

with a limited motility. The right disc was hyperaemic, with a blurred margin, and a bruit could be heard over the right eye. The clinical impression was of a haemorrhage into a teratomatous cyst or rupture of the cyst. A CT scan showed an enhancing right orbital mass consistent with the above diagnosis. Again routine laboratory evaluation was unremarkable. A right frontal craniotomy showed an infiltrative tumour in the muscle cone and optic canal. Biopsies and frozen sections revealed a malignant tumour. No attempt was made to resect it. Permanent sections showed a primitive epithelial tumour (Fig. 2). The final diagnosis was a malignant germ cell tumour. Tests for serum α -fetoprotein and chorionic gonadotrophin were negative. Over the subsequent 18 months she received interval therapy every three weeks consisting of vinblastine, bleomycin, and cis platinum alternating with cyclophosphamide, actinomycin D, and adriamycin. Radiation therapy totalled 4788 rads. Her last ophthalmological visit revealed questionable light perception on the right with a Marcus Gunn pupil but no evidence of recurrence of the tumour.

Discussion

This case represents two unusual aspects of congenital orbital-intracranial teratomas. First, the initial tumour was removed, with preservation of the eye and visual function. These tumours, although

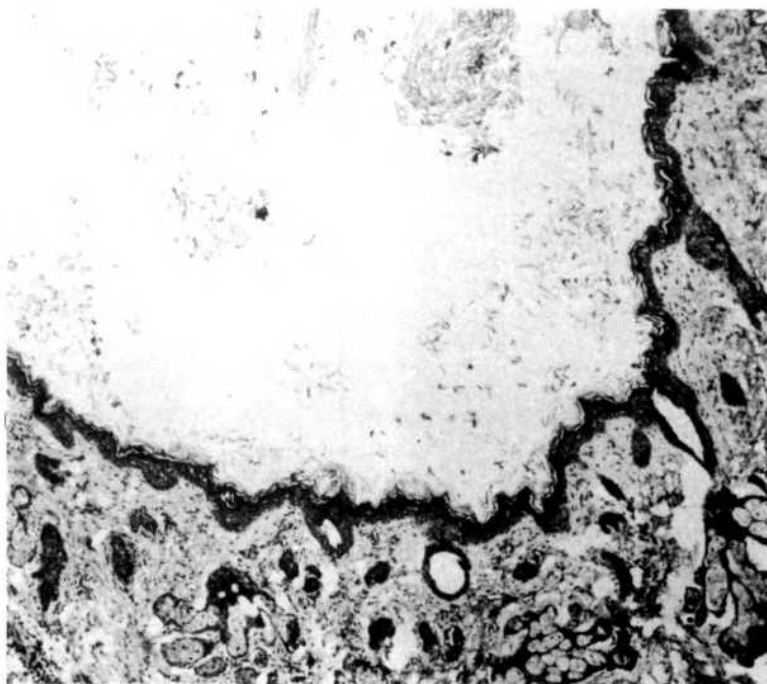


Fig. 1C A cystic area lined by squamous epithelium with skin appendages. (Haematoxylin and eosin, $\times 100$).

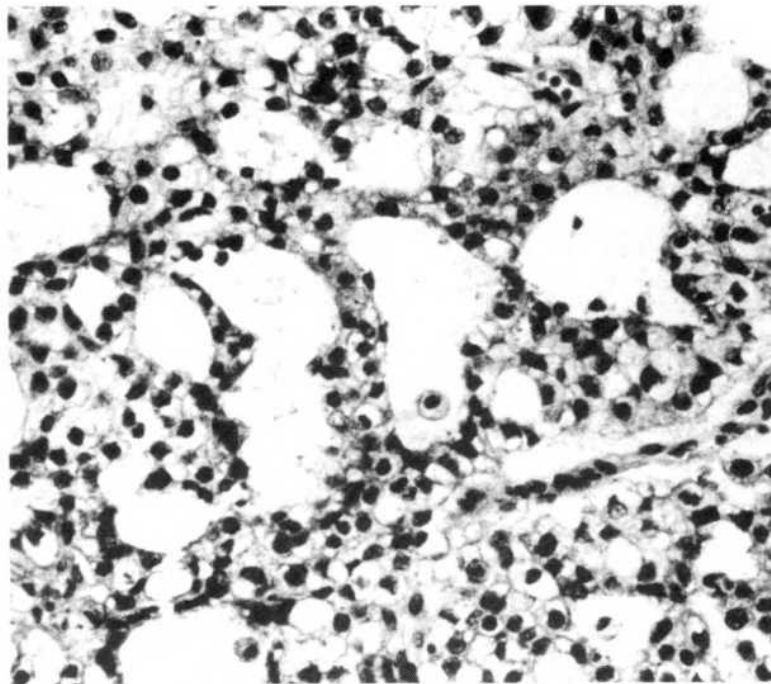


Fig. 2 Representative area of the primitive epithelial malignancy showing cystic or gland-like spaces. (Haematoxylin and eosin, $\times 400$).

considered benign, had previously been treated by exenteration. The change in surgical philosophy represented by this case has been discussed.¹ Secondly, a malignant tumour appeared in an area where a congenital teratoma had been considered to be completely excised.

Congenital teratomas confined to the orbit and congenital intracranial teratomas are both uncommon. Fifty-two congenital intraorbital teratomas had been reported up to 1980.¹ By definition an orbital teratoma does not extend beyond the confines of the orbit nor is it associated with teratomatous elements elsewhere in the cranium. The most complete review of reported intracranial teratomas of the newborn listed 24 and added another.² One of these infants had a teratoma of both the middle fossa and orbit.³

Teratomas are benign growths of mature and immature tissues which include derivatives of two or all three of the germ cell layers.⁴ Embryologically immature tissue in these tumours does not necessarily indicate malignancy. Malignant seminoma-like germ cell tumours are excluded from this discussion. True malignancy, as shown by the histological features of a carcinoma or sarcoma, has not been reported in intracranial teratomas of the newborn,² though such cases in children or adults have been noted.⁵ A single case of 'malignant teratoma' of the orbit is not sufficiently documented in the report to be accepted.⁶

Unanswered questions remain. Was this a malignant germ cell tumour that arose de novo or malignant degeneration in an incompletely excised teratoma? Teratomas in other locations are known to undergo malignant change, and the latter possibility seems most likely in this case. Since congenital orbital teratomas are usually excised, and intracranial teratomas are either excised or a cause of death in the newborn, the chance for malignant transformation is lessened. As a result of this, as well as their rarity, the true malignant potential of these tumours cannot be determined. This case demonstrates the long-term potential for malignancy in these teratomas, despite apparent curative resection, and the need for caution in expressing the prognosis.

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Retinal revascularisation in diabetic retinopathy

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SUMMARY The case history of a 33-year-old diabetic patient who has had diabetes for 24 years is presented. When first seen in 1975 he had bilateral proliferative retinopathy with new vessels in the retinal periphery. He had large areas of capillary non-perfusion lateral to the macula in the right eye associated with the new vessels. Nine years later, after extensive repeated photocoagulation, revascularisation of large areas previously not perfused were seen. The vessels are in the plane of the retina and do not have the appearance of new vessels.

Capillary non-perfusion is a sign of ischaemia in diabetic retinopathy. It is a precursor and is thought to be a stimulus for the formation of new vessels in the retina.¹ While revascularisation of small areas of capillary non-perfusion have been recorded,² when large areas are involved the condition is thought to be irreversible. We report on a patient with proliferative retinopathy in whom revascularisation of a large area followed extensive photocoagulation.

Case report

A 33-year-old male patient was first seen in the Retinopathy Clinic at the Hammersmith Hospital in 1975. He had been a diabetic since the age of 9 years. Initially he was treated with a single daily dose of PZI and soluble insulin, but since 1969 he had had twice daily Rapitard in a total dose of 152 units daily. He was on a 160 gram carbohydrate diet. During the previous year his hitherto poor diabetic control improved, so that most of his urine tests were between 0 and 1/4%.

He had symptoms of peripheral neuropathy and stiffness in his fingers, but was otherwise well. He noted spots in front of his eyes and intermittent blurring of vision for about one year; this precipitated his referral to the clinic.

On examination he was of ideal body weight. He had a normal blood pressure of 120/75 mmHg, normal peripheral pulses, absent ankle jerks, and reduced vibration senses. Investigations showed a trace of proteinuria, normal blood urea of 6 mmol/l, creatinine 91 μ mol/l, and normal serum proteins. The only significant abnormality was in his eyes.

Visual acuity (VA) was 6/6 in both eyes uncorrected and the intraocular pressure was 15 mmHg. He had no cataract or rubeosis. He had extensive peripheral new vessels in all four quadrants of his retina (NVE) with areas of fibrous tissue proliferation but no new vessels on the disc (NVD) (Fig. 1a). A fluorescein angiogram confirmed extensive new vessels and demonstrated extensive areas of capillary non-perfusion lateral to the macula (Figs. 1b and 1c).

Because of the symmetry of the two eyes and because at that time the benefits of photocoagulation were not proved, he was advised to join the British Multicentre Study in which one eye was treated by

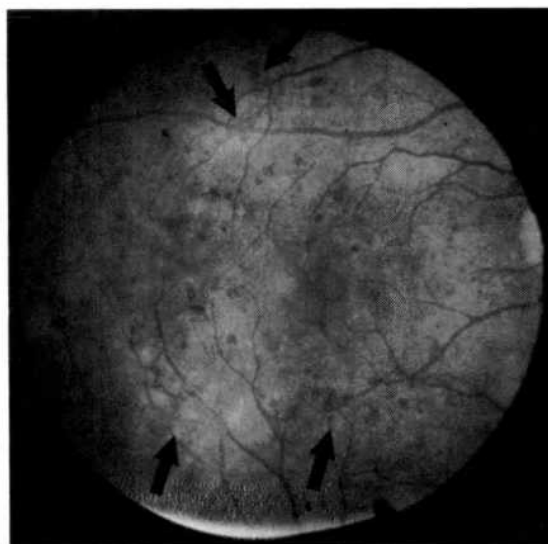


Fig. 1a Right macular area showing multiple microaneurysms, haemorrhages, and new vessels (arrows).

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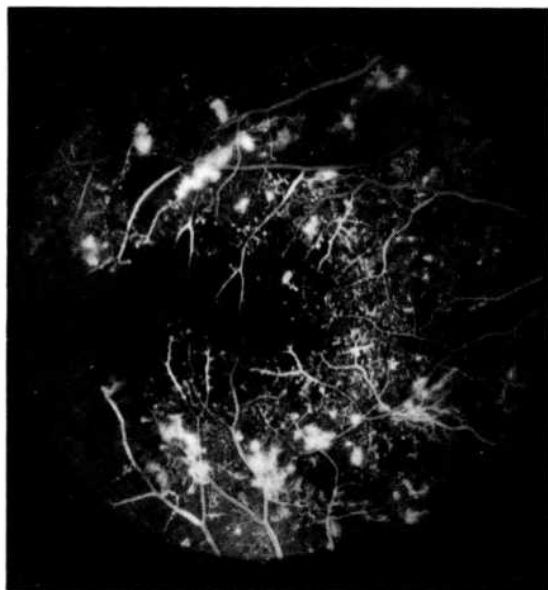


Fig. 1b Fluorescein angiogram of area shown in Fig. 1a, in capillary phase. There is widespread leakage from new vessels. There is no capillary perfusion lateral to the macula.

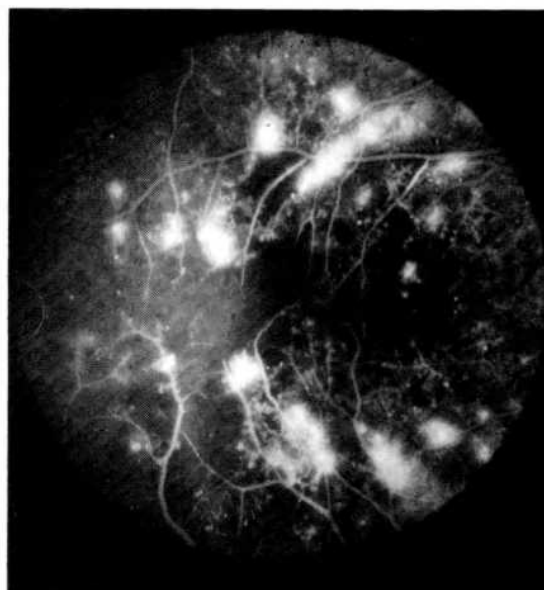


Fig. 1c Same as Fig. 1b, but late phase shows that perfusion lateral to the macula is absent, not delayed.

xenon arc while the other eye was followed up as an untreated control. The right eye was chosen for treatment by a randomisation procedure and had several treatment sessions under retrobulbar anaesthesia with the xenon arc. In all he had 520 xenon arc

burns in the right eye between 1975 and 1977. In 1977, because of a haemorrhage from the new vessels in the left eye, this was also treated. In December 1978 his VA was 6/12 on the right and 6/6 on the left. The new vessels had improved and others had been replaced by fibrous tissues. The visual loss was thought to be due to preretinal fibrosis.

Between 1978 and 1983 he developed further new vessels in both eyes, especially in the left, including NVD and several preretinal haemorrhages. He needed further extensive treatment of panretinal photocoagulation, now with the argon laser. He had 1450, 500 μ m spot size burns on the right and almost 4000 in the left. In 1983 the VA was 6/12 on the right and 6/9 on the left. Both retinæ were now more quiescent and fluorescein angiography showed striking revascularisation lateral to the macula. No further treatment was necessary.

The patient was last seen in February 1985. His diabetic control was then excellent on twice daily Actrapid and Monotard insulin, total daily dose of 50 units. His glycosylated haemoglobin (HbA1) has been between 7.7% and 9.7% in the last three years (upper limit of normal 8%). His blood pressure had risen to 150/88 mmHg. He had no proteinuria; urea was 3.6 mmol/l and the creatinine 88 μ mol/l. His visual acuity was 6/18 and L 6/9. The retinopathy had not changed significantly in the last two years, though some activity was still present (Figs. 2a–c). The vessels seen on angiogram were in the plane of the

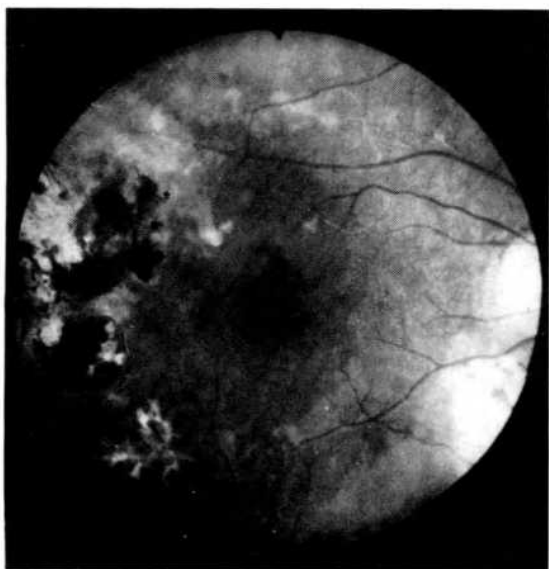


Fig. 2a Right macular area 10 years later after extensive photocoagulation, showing quiescent retinopathy with little fibrous tissue.

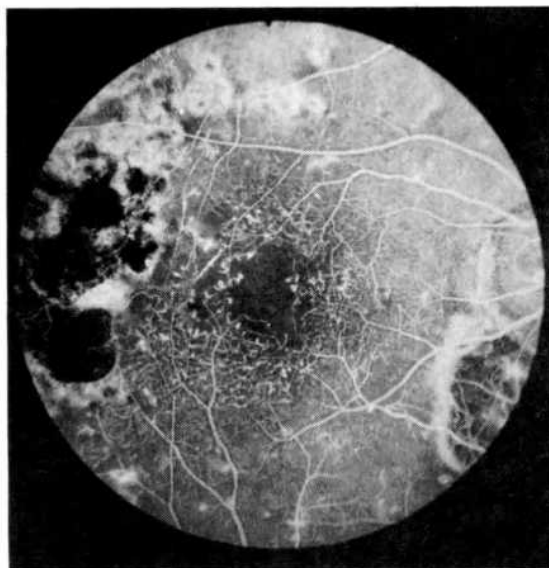


Fig. 2b Fluorescein angiogram shows revascularisation lateral to the macula in the plane of the retina.

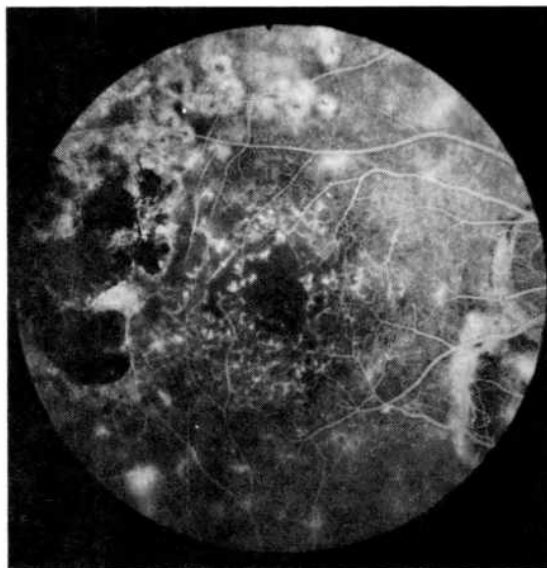


Fig. 2c Late pictures show leakage from fibrous tissue and minimal leakage from capillaries.

retina and did not have the appearance of new vessels.

Discussion

This case demonstrates the occurrence of capillary revascularisation in a previously avascular area of the retina in a patient with advanced diabetic eye disease after extensive photocoagulation. Revascularisation of non-perfused areas has been demonstrated previously in experimental animals after exposure to high intensity light³ and branch vein occlusion.⁴ It has also been noted in humans in retinal branch vein occlusion.^{5,6} Recently a patient with radiation retinopathy in both eyes has been described in whom partial reperfusion of the capillary bed occurred.⁷

In the natural history of diabetic retinopathy capillary non-perfusion is one of the most important features, since the sight-threatening lesions of macular oedema and neovascularisation are secondary to capillary occlusion. Most areas of capillary closure are irreversible and enlarge progressively. It has been reported that in some areas of capillary closure, associated with cotton wool spots, capillaries may reopen.⁸ In a recent report Muraoka and Shimizu² describe both 'recanalisation' and 'intra-retinal neovascularisation' to describe the vessels that appeared in their patients. However, in that study all patients initially had non-proliferative retinopathy and new vessels developed subsequently. In the patient presented here there was

extensive non-perfusion and proliferative retinopathy at presentation. The revascularisation occurred after extensive photocoagulation. The stimulus for the large area of revascularisation is not known. However, in a recent study, Marshall *et al.*⁹ have demonstrated in experimental photocoagulation proliferation of capillary and venous endothelium. This must be the result of the photocoagulation, though it is not clear whether it is a reaction to pigment epithelial damage or transfer of a vasoproliferative substance from the choroid. The findings reported here raise the interesting possibility that, at least in some patients, there may be a partially reversible component in diabetic retinopathy even at advanced stages of the condition.

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External diathermy treatment of proliferative diabetic retinopathy with vitreous haemorrhage

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SUMMARY Sixty-six cases of advanced proliferative diabetic retinopathy were treated by external diathermy. The eyes had extensive fibrovascular proliferations growing into the vitreous. All had some blood, recent and old, in the vitreous. The vitreous was extremely degenerated and retracted. All the patients had inadequate diabetic control. More than half were hypertensive, with reasonable medical control, while a few had some degree of renal failure, with lower limb oedema. None of the cases were suitable for photocoagulation. Thirty-two control eyes were followed up together with the treated eyes for one to eight years. Of 53 eyes of patients with maturity onset diabetes 28 improved, 12 remained unchanged, and 13 deteriorated. Only two eyes developed neovascular glaucoma, while eight of 13 eyes of patients with juvenile diabetes improved. Of the control eyes, one regressed spontaneously, six remained unchanged, and 25 deteriorated. Of these 25 eyes eight developed traction detachment, 10 suffered relentless attacks of vitreous haemorrhage, and seven developed neovascular glaucoma. External diathermy appears to be a logical approach to cases which could not be treated by either photocoagulation or vitrectomy.

At present the major lines of treatment for proliferative diabetic retinopathy (PDR) are photocoagulation therapy and vitrectomy procedures. Buckling techniques have also been applied to cases of traction detachment, due to diabetic retinopathy.¹ The efficacy of photocoagulation becomes progressively less with the more advanced stages of PDR owing to fibrovascular proliferation and traction detachment. This line of therapy is out of the question if considerable amounts of blood are present, particularly in the vitreous gel. Nor can it be applied to cases with marked corneal or lens opacities.

There remain only two possibilities for retinal coagulation, namely cryotherapy and external diathermy. No results are available of a controlled study on the effects of external diathermy for cases of PDR in which photocoagulation treatment is impossible and vitrectomy procedures are not indicated. Wessing and Bockenhoff² reported on the effect of treatment by intrascleral diathermy and have observed that haemorrhages into the vitreous are usually quickly absorbed. We made a preliminary report on the beneficial effects of external diathermy on the course of PDR with vitreous haemorrhage.³

Cryotherapy has also been tried for such cases,⁴ but there is no definitive study on this line of treatment.

The natural history of such cases is unpredictable. A minority start to regress and continue to dry up and quieten down both as regards the vitreous blood and the fibrovascular elements; even the traction detachment regresses. Fibrous arcs, with limited detachment, persist in such cases. The patient retains some walking vision and occasionally may enjoy aided reading ability.³

However, when the course is regressive, whether spontaneously or following external diathermy treatment, more glial formations have been observed, often with traction detachment. The last was associated with extensive vascular sheathing and attenuation, with apparently extensive ischaemic areas marked by fibrovascular formations at their limits. This condition was more marked in the untreated cases and was followed either by neovascular glaucoma or by optic atrophy (see 'Results' below).

However, most of the untreated cases (25 out of 32, i.e. 78%) continued to progress to more fibrovascular proliferations, and then developed either extensive traction detachment or a state of old, persistent vitreous haemorrhage.

Many of these eyes developed neovascular glaucoma and cataract, with an unsightly painful eye

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(7 out of 32, i.e. 22%). Of the late developments rhegmatogenous retinal detachment and retinoschisis appear to be the result, with more fibrosis and more vitreous degeneration and retraction, resulting in both static and dynamic vitreous traction.

Vitreotomy techniques are a great advance in dealing with some cases of old-standing vitreous haemorrhage and of traction retinal detachment. But such elaborate surgical approaches, including the separation, cutting, and circumscision of epiretinal membranes,⁷ are not indicated early in the course of progressive diabetic retinopathy with recurrent attacks of vitreous haemorrhage and active neovascular activity.

Material and methods

PATIENTS

Sixty-six eyes of PDR were treated with external diathermy coagulations. Together with 32 control eyes, mostly the other eye of treated patients, they were followed up for one to eight years. The duration of diabetes ranged from five to 35 years. Thirteen cases had type I diabetes, and their ages ranged from 20 to 35. Fifty-three cases were of maturity onset or type II diabetes, with ages of 45 to 70 years. The control of diabetes was poor and irregular in all cases. Forty-three cases were receiving antihypertensive drugs, with reasonable control of their hypertension.

Their visual acuity ranged from 1/60 to 6/24.

Anterior segment examination did not show any iris new vessels on slit-lamp examination. The vitreous was found to be retracted and contracted, with vitreovascular and vitreogelial adhesions in all cases where it could be satisfactorily examined.

Fifty-six cases had varying amounts of vitreous blood, but the fundus could be visualised to allow reliable evaluation of the fundus changes. Ten cases presented with massive, recent, bright red vitreous blood. Six cases had partial retinal detachment involving more or less than one quadrant of the retina.

Eight cases had lower limb oedema, with marked albuminuria and lid puffiness.

The 66 treated cases shared the following features. All had extensive fibrovascular proliferations arising from the disc and from the retinal surface. The areas of surface proliferations were several disc diameters, while the disc vessels were already pulled into the vitreous for varying distances. More than half of the cases had extrapapillary retinovitreal proliferations. All had vitreous blood in quantities which ranged from an amount that allowed reasonable visualisation of fundus details (56 cases) to massive vitreous blood that did not allow any view of the fundus (10 cases). The last group of cases had either been under

our care before the attack of vitreous haemorrhage, and therefore had a record of the stage of their PDR, or were studied only by ultrasonography, providing data on the vitreous echos, vitreous membranes, and the position of the retina. The electroretinogram (ERG) was also done in these cases, in some with a bright flash.

Twelve cases had been treated by photocoagulation, xenon or argon laser, before the attack of vitreous haemorrhage.

Thirty-two control cases had the same features as the treated cases and were randomly chosen. They received aspirin tablets only in addition to their antidiabetic treatment, with special insistence on as much attention as possible to diet and diabetic control and the avoidance of straining efforts.

Fasting blood sugar values ranged from 120 to 350 mg/dl (6.7–19.4 mmol/l). Six cases had acetone in their urine when first seen, but only two of these women had repeated acetonuria in the follow-up. Four of them were in the treatment group.

METHOD

Seventy to 80 1 mm diameter applications of 50–60 mA for 2 seconds were enough to produce a yellowish white reaction in all cases, with reasonable fundus visibility. The coagulations were placed over the upper and lower temporal quadrants, above and

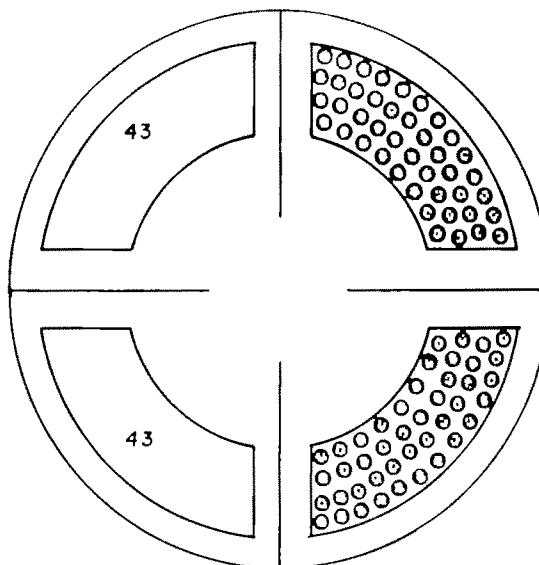


Fig. 1 Shows the pattern of diathermy applications each 50–60 mA for 2 seconds. Forty-three 1 mm diameter applications placed over upper and lower temporal quadrants, above and below the lateral rectus muscle; parallel rows, each row staggered in relation to the next.

below the lateral rectus muscle, sparing the temporal long posterior ciliary artery. They were made in rows parallel to the equator, each row being staggered in relation to the next (Fig. 1).

In nine cases the operation was repeated over the nasal quadrants, again sparing the nasal long posterior ciliary artery. Twelve cases had had previous panretinal photocoagulation (PRP) (Table 3).

At first the Hamblin ophthalmic diathermy unit was used, but later the unipolar radiofrequency Mira diathermy unit was used at a setting of 5–6 intensity for 1–2 seconds. When visibility was reasonable, control of the intensity of coagulations was possible. Overreactions were always avoided; overshrinkage of the sclera was not allowed, especially over thin scleral areas. The raised ocular tension was controlled by repeated paracentesis; in all cases the globe was left with firm tension. I made sure that the retinal vessels were at least pulsating at the end of the coagulation procedure. In the cases where the fundus was not visible the tension was kept below 35 mmHg.

Results

Of 53 cases (Table 1) of maturity onset diabetes 28 (53%) improved, with visual results attained between 1/60 and 6/24. Twelve eyes (22%) remained almost unchanged, while 13 eyes (25%) steadily deteriorated to more fibrosis and traction detachment. It was observed, however, that only two of these suffered repeated attacks of vitreous haemorrhage, and only two eyes developed neovascular glaucoma (less than 4%). Five ended in traction detachment (less than 10%) and four showed optic atrophy and vascular sclerosis.

Of the cases treated again (nine eyes) six improved and three deteriorated, while of the 12 eyes that had previous PRP 10 improved and two got worse (Table 2).

Of 13 eyes of juvenile (type I) diabetes treated, eight (61.5%) improved, the retinopathy quietening almost completely, with few white retinovitreal and papillovitreal white bands. Five cases deteriorated, two suffering further attacks of vitreous haemorrhage, two traction detachment, and one ending in neovascular glaucoma.

COMPLICATIONS

Ocular hypertension followed the diathermy applications in all cases and, unless controlled with repeated paracentesis, could lead to acute ischaemic optic atrophy. Choroiditis and vitritis occurred in four cases, while reactionary retinal detachment was observed in three. This complication took several days to clear up; only one case took more than one week to disappear.

Table 1 Numbers and types of diabetic cases treated with external diathermy and results of treatment.

<i>Treated cases</i>		
<i>Total</i> 66	<i>Type II</i> 53	<i>Type I</i> 13
Improved	28	8
Unchanged	12	0
Deteriorated	13	5
VH	2	2
TD	5	2
NG	2	1
OA	4	0

VH=vitreous haemorrhage. NG=neovascular glaucoma.
TD=traction detachment. OA=optic atrophy.

Table 2 Course of 32 control cases in this study

	<i>Cases</i>	<i>Improved</i>	<i>Deteriorated</i>
Retreatment	9	6	3
Previous PRP	12	10	2

Table 3 Course of retreatment cases and those that had previous panretinal photocoagulation (PRP)

<i>Control cases</i>		
<i>Total</i> 32	<i>Type II</i> 27	<i>Type I</i> 5
Spont. regression	1	0
Unchanged	6	0
Deteriorated	20	5
VH	9	1
TD	6	2
NG	5	2
OA	0	0

VH=vitreous haemorrhage. NG=neovascular glaucoma.
TD=traction detachment. OA=optic atrophy.

Of 32 control cases (Table 3) five were of type I diabetes and 27 of type II or maturity onset diabetes. Only one maturity onset cases was observed to have regressed spontaneously, with quietening down of the neovascular activity and clearing of the vitreous blood. More gliosis was observed over the years, but that did not appear to alter significantly the visual function. Only six cases (22%) of this type of diabetes remained almost unchanged, while 20 (74%) deteriorated. Of the 20 eyes nine continued to bleed in the vitreous, six developed extensive traction detachment (22%), and five ended up in neovascular glaucoma (18.5%). All five eyes belonging to juvenile patients steadily deteriorated, with repeated attacks of vitreous haemorrhage in one eye, traction detachment in two, and neovascular glaucoma in two.

Discussion

External diathermy appears to be the logical treatment of proliferative retinopathy when photocoagulation is impossible. It is particularly indicated for patients with PDR previously treated by photocoagulation who sustain an attack of vitreous haemorrhage and a flare-up of the fibrovascular activity, which would demand more retinal coagulations. This condition had quietened in 10 out of 12 such cases, astonishingly quickly. In addition further coagulation with the xenon arc or argon laser photocoagulators became possible after the rapid absorption of vitreous blood following diathermy coagulations (13 cases). Alternatively, further diathermy coagulation can still be done (9 cases).

Massive vitreous haemorrhage associated with PDR is rarely absorbed spontaneously and often recurs before enough absorption has taken place. This precludes the possibility of retinal photocoagulation and delays effective treatment. Such cases responded surprisingly quickly to diathermy treatment. In some cases after only 24 hours the absorption of the vitreous blood was remarkable. This was especially so with small fibrovascular formations.

Although the trend at present is towards earlier vitrectomy for vitreous haemorrhage, this procedure is never indicated for recent recurrent vitreous haemorrhage. This leaves us with only one possibility—namely external diathermy. I have not met with any serious complications of this treatment, nor was it apparent that such treatment adversely affected the course of PDR. It was of no use in certain cases. Only 13 out of 53 eyes treated continued to deteriorate, and only two out of these developed neovascular glaucoma, less than 4%. Of 32 control cases 25 eyes (78%) deteriorated, and seven of these developed neovascular glaucoma.

Serious complications have been reported when vitrectomy was performed on such cases—49% in the group of cases treated by Tolentino and Freeman.⁶

No serious complications were encountered with our technique of transcleral choroidoretinal coagulation with local steroid treatment. Routine subconjunctival steroid and postoperative topical steroid were administered. Rarely systemic steroid therapy had to be instituted.

We have combined the buckling technique without

drainage of subretinal fluid¹ with external diathermy for PDR with traction detachment, and did paracentesis to control the tension, with good results. But we found that buckling and external diathermy with drainage were more effective in these cases (the results are not included in this study).

PROGNOSTIC FACTORS

A fairly good prognosis was associated with less florid PDR and less fibrovascular density. It was also better with less vitreous blood of less duration. Better visual prognosis was also associated with a good visual acuity before the attack of vitreous haemorrhage and with favourable ultrasonographic findings.

CONCLUSION

A controlled study of the role of diathermy treatment for diabetic vitreous haemorrhage and partial traction detachment has shown that a beneficial effect was observed in more than half of the cases. This line of treatment afforded a sound alternative to retinal photocoagulation and allowed the subsequent application of photocoagulation to a number of eyes. It also reduced the incidence of neovascular glaucoma considerably in the eyes that continued to deteriorate (two out of 53 cases, less than 4%) after diathermy treatment compared with seven out of 25 eyes that deteriorated without treatment (22% of 32 cases).

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Bacteriology and tear protein profiles of the dry eye

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SUMMARY The concentrations of tear lysozyme, lactoferrin, ceruloplasmin, IgA, and IgG have been estimated in patients with dry eyes at the same time as semiquantitative bacterial culture was performed of the conjunctivae and lids. Staphylococcal isolations were quantified and biotyped. There was no increased conjunctival colonisation by any particular biotype of *Staphylococcus aureus* or *Staph. epidermidis*, and similar numbers of conjunctivae were sterile as in controls (33%); neither were any pathogens such as pneumococci or haemophili isolated. We consider that the conjunctiva of the dry eye, without the lacrimal secretion components of lysozyme and lactoferrin, has an alternative protective antibacterial mechanism which is derived from serum proteins via chronically inflamed vessels.

The dry eye is often considered to be infected with staphylococci,¹ partly because they are easy to culture from the lids and conjunctivae² and partly because of reduced amounts of tear lysozyme being present. However, the normal eye is usually colonised with certain types of staphylococci, so that commensals need to be distinguished from those with a pathogenic role. Different subtypes of staphylococci have recently been investigated in both normal persons and patients with chronic blepharitis by a semiquantitative culture technique.³ Certain biotypes of staphylococci were shown to exist in large numbers on normal lids and conjunctivae while only 33% of normal conjunctivae sampled were sterile. This same technique has now been used to culture organisms from patients with either keratoconjunctivitis sicca or 'questionably dry' eyes in order to investigate how the bacterial flora differs in these patients from that of normal persons and whether it relates to altered concentrations of lysozyme, lactoferrin, ceruloplasmin, or immunoglobulins found in their tears.

Patients and methods

Results from 66 normal volunteers, aged 20-80 and previously described,^{3,4} have been compared with

those from patients. Both groups were sampled for tear proteins and microbial culture over the same period by identical techniques. Both eyes were sampled of six patients with well established keratoconjunctivitis sicca, as were both eyes of 13 patients who were considered 'questionably dry' and who also had reduced levels of tear lysozyme and lactoferrin.

The bacteriological sampling technique has been described previously³ together with the simple Baird-Parker scheme used to subdivide *Staphylococcus epidermidis* isolates into five biotypes. The enzyme-linked immunosorbent assay (ELISA) method developed to measure the concentration of the various tear proteins has also been given,³ as well as the effect of age on normal levels.⁴ This has allowed us to compare the tear protein concentrations for each patient with expected normal values for that age.

Results

TEAR PROTEIN PROFILES

In the sicca patients both tear lysozyme and lactoferrin concentrations were more than 2 standard deviations below the mean of normal persons ($p < 0.05$), while the ceruloplasmin concentration was significantly increased ($p < 0.05$) above normal in six out of 12 eyes (Fig. 1). Amounts of IgA were in the low normal range, and were reduced below 2 standard deviations from the mean in three out of 12 eyes, while IgG was greatly increased in eight out

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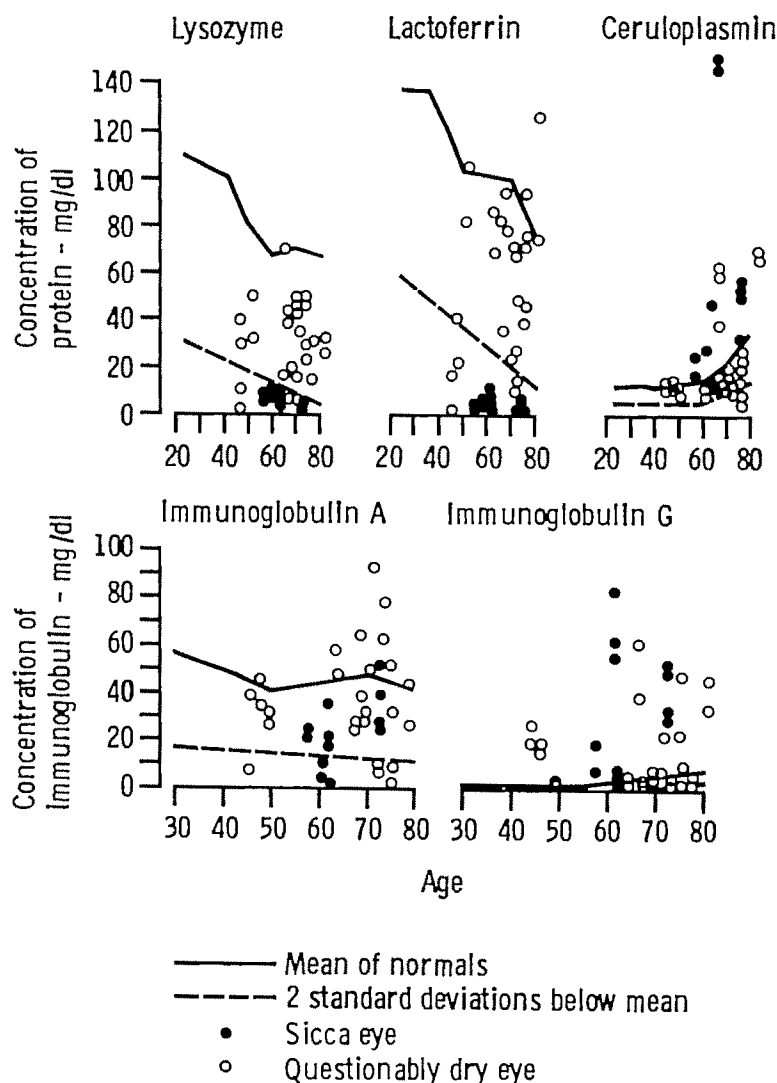


Fig. 1 Tear protein levels in sicca and questionably dry eyes.
(SI conversion: $\text{mg/dl} \times 0.01 = \text{g/l}$).

of 12 eyes. In the patients with 'questionably dry' eye both tear lysozyme and lactoferrin were in the low normal range, and significantly low ($p < 0.05$) in four and five eyes respectively (Fig. 1). The tear ceruloplasmin concentrations were in the normal range except in two eyes greater than 2 standard deviations from the normal mean and two eyes below this limit. The IgA was within the normal range except in five eyes greater than 2 standard deviations below the mean. IgG was found in the normal range for 15 eyes but significantly raised ($p < 0.05$) for 11 eyes.

BACTERIOLOGY

Results of bacterial isolations from lids and conjunctivae are given qualitatively in Table 1 and

quantitatively, for staphylococcal isolates, in Table 2. They show that a heavy growth of *Staph. aureus* was present in only one patient (both eyes) but not in others, while there was little difference with *Staph. epidermidis* between the patients and normal persons.

Discussion

The reduction found in tear lysozyme concentration in the patients with dry eye confirms earlier work.¹ This decrease parallels the severity of the condition, so that in patients with severely dry eye the lysozyme concentration falls to zero. A similar reduction has been demonstrated for lactoferrin, whose correlation with lysozyme is impressive. Such correlation has

Table 1 Percentage isolations of bacterial flora from each group

	Normal eyes* (n=66)		Sicca eyes (n=12)		Questionably dry eyes (n=26)	
	Lid %	Conj. %	Lid %	Conj. %	Lid %	Conj. %
Staph. aureus (type I)	5	2	17	17	0	0
Staph. epidermidis (type II/III)	47	33	67	25	65	31
Staph. epidermidis (type IV/V)	8	14	17	17	38	8
Staph. epidermidis (type VI)	6	2	25	0	4	0
Micrococcus	21	5	0	0	8	0
Diphtheroids	31	18	17	0	8	0
Str. pneumoniae	0	0	0	0	0	0
Str. viridans	0	0	0	0	8	8
Neisseria sp	5	2	0	8	12	0
Haemophilus sp	2	0	0	0	0	0
Coliforms	5	0	0	0	0	0
Pityrosporum sp	8	0	0	0	8	0
No growth	17	33	0	25	12	58

* Seal *et al.*³

also been found by Janssen and van Bijsterveld, using polyacrylamide-gel electrophoresis.⁵ In an earlier study⁴ we found a correlation between amounts of lysozyme and lactoferrin, also assayed by ELISA, at $r=0.60$ ($p<0.01$) in the normal eye. The combined reduction of lysozyme and lactoferrin, both potent antibacterial proteins, could be considered to compromise the eye, increasing the risk of local infection. However, we found greatly increased tear IgG in 19 out of 38 eyes examined and increased tear ceruloplasmin in eight eyes. IgA levels were reduced in only eight eyes. The increased ceruloplasmin concentra-

tion may be due to tear concentration as well as its secretion from chronically inflamed conjunctival vessels. Increased tear IgG is probably from the same source, and, while complement components were not assayed, they can be expected to be increased as well.

The various antibacterial roles of these inhibitors in biological secretions have been reviewed,⁶ and complement and IgG have been shown to have definite antibacterial activity, but conditions like the dry eye were not considered. However, these conditions can be produced experimentally now that the concentrations of each protein are known. They

Table 2 Quantitative bacteriology results for staphylococci isolated from lids and conjunctivae

	% Isolations in each group					
	Normal eyes* (n=66)		Sicca eyes (n=12)		Questionably dry eyes (n=26)	
	Lid	Conj.	Lid	Conj.	Lid	Conj.
Staph. aureus (type I)						
+/-	5	2	0	0	0	0
+	0	0	0	0	0	0
++	0	0	17	17	0	0
Staph. epidermidis (type II/III)						
+/-	3	12	0	0	12	8
+	33	21	33	25	38	23
++	11	2	42	0	15	0
Staph. epidermidis (type IV/V)						
+/-	0	5	0	9	12	4
+	6	9	17	9	19	4
++	2	0	0	0	8	0
Staph. epidermidis (type VI)						
+/-	6	0	25	0	0	0
+	0	2	0	0	0	0
++	0	0	0	0	0	0

* Seal *et al.*³

could then be tested for bacterial inhibition against isolates from a patient's lid flora with dilutions of the patient's own serum as a source of IgG antibody and complement, to mimic secretion from inflamed vessels. If it can be shown that these components, IgG and complement, have antibacterial activity against lid isolates, then this would support our hypothesis that in the patient with dry eye these components replace the antibacterial activity of the decreased levels of lysozyme and lactoferrin.

Bacteriological assessment of the conjunctiva is best performed by a semiquantitative method.⁷ However, any method is slightly affected by 'sample error' when collections are made from the eye unless a biopsy is taken and processed whole, but that of Cagle and Abshire is worthy of consideration.⁸ They sampled conjunctivae with soluble alginate swabs which they then dissolved in a measured volume of buffer so as to gain a numerical count. They then compared a test result with an expected numerical value for normal flora. While this must be considered ideal for investigating an individual patient, particularly for chronic staphylococcal infection, it is not necessary when a pathogen such as pneumococcus is isolated which is known to be *absent* from the uninfected eye. However, their method can be usefully applied to the investigation of chronic infection in a dry eye, particularly to distinguish between staphylococcal colonisation and infection. Differentiation of *Staph. epidermidis* into separate biotypes is also useful. We have used the British classification system, based on Baird-Parker (1963), as opposed to the American system, based on Kloos and Schleifer (1975); both have been reviewed and compared recently by Marples.⁹

Our qualitative results show that the conjunctivae were sterile by our culture methods in 33% of normal eyes, 25% of sicca eyes, and 58% of 'questionably dry' eyes. In those patients from whom bacteria were isolated there were no pathogens such as *Streptococcus pneumoniae*, or *Haemophilus influenzae*. There was no difference between normal persons and patients in the conjunctival isolation rates of *Staph. epidermidis* types II/III, IV/V, and VI, which thus colonise the conjunctivae of dry eyes in the same amounts as normal eyes. The lid flora differed in sicca eyes, with *Staph. aureus* being present as a heavy growth in only one patient, but without pus being present, compared with none in the normal persons, and with *Staph. epidermidis* type II/III being present as a heavy growth in 42% compared with 11% in normal persons. However, in another study this type (II/III) was not found to be associated with

chronic non-ulcerative blepharitis.³ The reason for increased numbers of *Staph. epidermidis* type II/III in the lids of sicca patients is not clear, but a heavy growth did not occur on the conjunctivae. We have thus found little evidence to support either *Staph. aureus* or *Staph. epidermidis* being more pathogenic in the dry than the normal eye.

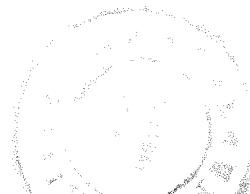
Janssen and van Bijsterveld have recently investigated various tear proteins in their patients with dry eye and found similar reductions in lysozyme and lactoferrin. They too recorded very few clinical infections in 300 of their patients but did not carry out bacteriological studies.¹⁰ This supports our hypothesis that there is local antibacterial activity in the conjunctiva of the patient with dry eye.

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Scrolls of Descemet's membrane as unusual giant nodules on the posterior cornea: histochemical and ultrastructural findings

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SUMMARY Unusual giant nodules on the posterior surface of Descemet's membrane were observed in two out of over 400 corneae examined during routine histopathological reporting. Both of the patients, a 60-year-old man and a 26-year-old woman, had histories of corneal trauma. Neither was associated with chronic keratitis or corneal dystrophy. Light microscopy showed these nodules to be composed of material resembling Descemet's membrane. Histochemical and electron microscopical preparations identified oxytalan fibres within the outer layers of the nodules. These fibres are not a feature of the normal adult Descemet's membrane. The findings are discussed and compared with other nodular lesions of Descemet's membrane.

Descemet's membrane is an apparently homogeneous structure that is produced by the corneal endothelium. Electron microscopy, however, has shown that it consists of two distinct layers—an anterior, organised banded zone and a posterior, relatively unorganised, non-banded zone that increases in thickness with age.^{1,2} Small islands of 100 nm wide-spacing collagen may be observed within the periphery of the posterior layer.³ Hassal-Henle warts are focal thickenings on the posterior surface of the peripheral Descemet's membrane; they are considered to be related to aging.^{3,4} Similar nodular thickenings in the central cornea are a feature of Fuchs's late hereditary endothelial dystrophy, while focal fusiform nodular swellings are seen in posterior polymorphous dystrophy.⁵ Recently Scattergood *et al.*⁶ described giant nodules that consisted of scrolls of Descemet's membrane in a patient with syphilitic interstitial keratitis.

If Descemet's membrane ruptures, the severed edges tend to roll posteriorly as if under a state of tension. This elastic property of Descemet's membrane is well known, though typical elastic fibres have not been demonstrated within it.^{2,3,7} However, Heathcote *et al.*⁸ biochemically identified desmosine and isodesmosine in bovine Descemet's membrane.

These lysine-derived amino acids are considered to be unique to elastin.⁹

The mature elastic fibre is composed of two morphologically and biochemically different elements:^{9,10} a central amorphous elastin core, which may amount to 90% or more of the fibre volume, and a predominantly peripheral array of 10–16 nm diameter, tubular appearing, microfibrils. Oxytalan fibres¹¹ exist as bundles of the glycoprotein microtubules alone. They correspond to the earliest identifiable stage of elastogenesis.¹² Elaunin fibres,¹³ the third member of the elastic fibre system, represent an intermediate stage of development between oxytalan and mature elastic, being seen as bundles of microtubules with infiltrating islands of amorphous material.¹⁴ The histochemical properties of the elastic fibre family are outlined in Table 1.

As with mature elastic, neither oxytalan nor elaunin fibres are demonstrable in the normal adult human cornea.⁷ Oxytalan fibres though, have been observed as a transient feature of the young Descemet's membrane of man⁷ and cat.¹⁵ They have also been identified within the retrocorneal fibrous tissue layer produced by endothelial cells in examples of Fuchs's endothelial dystrophy,^{16,17} congenital endothelial dystrophy,¹⁸ posterior polymorphous dystrophy,¹⁹ and advanced keratoconus.²⁰ The production of oxytalan fibres in later life, as seen in these

Table 1 Summary of the histochemical properties of oxytalan, elaunin, and mature elastic fibres

Methods	Fibre type		
	Mature elastic	Elaunin	Oxytalan
Verhoeff iron haematoxylin	+	-	-
Ox-Verhoeff iron haematoxylin	+	-	-
Gomori aldehyde fuchsin	+	+	-
Ox-aldehyde fuchsin	+	+	+
Elastase-Verhoeff iron haematoxylin	A	-	-
Elastase-Aldehyde fuchsin	A	A	-
Elastase-ox-aldehyde fuchsin	A	S*	S
Ox-elastase-aldehyde fuchsin	A	A	A

Ox=section oxidation in 10% Caroat - =unstained + =stained
S=stained (little or no change) A=abolished staining

*Staining of amorphous core abolished by elastase but peripheral microfibrils induced to stain by oxidation

corneal diseases, may be the result of derepression of fetal genes.

In a review of more than 100 corneal discs and over 300 eyes which were removed for a variety of reasons we found two examples of giant nodules on the posterior surface of Descemet's membrane which were morphologically similar to those of Scattergood *et al.*⁶

The present communication describes the distribution of elastic related fibres in our two cases with giant nodules of Descemet's membrane. The findings are compared with those of other nodular lesions of Descemet's.

Materials and methods

Specimen 1 was an eye enucleated for malignant melanoma of the choroid. The patient was a 60-year-old man who had a history of perforating injury to the cornea during childhood.

Specimen 2 was an eye from a 26-year-old woman. It was painful and blind as a consequence of long-standing raised intraocular pressure (congenital glaucoma). There was evidence of previous iridectomy.

Neither of the patients had clinical evidence of either corneal dystrophy or chronic keratitis.

LIGHT MICROSCOPY

Both eyes were fixed in 10% formal saline, processed into paraffin wax, and sectioned at a thickness of 6 µm.

Sections were dewaxed, hydrated, and stained by the following methods:

Mayer's haematoxylin and eosin for routine examination.

Verhoeff's iron haematoxylin for mature elastic fibres.

Gomori's aldehyde fuchsin for elaunin and mature elastic fibres.

Aldehyde fuchsin following oxidation in 10% caroat for 60 min or peracetic acid for 30 min¹⁰ to demonstrate oxytalan fibres in addition to elaunin and elastic. Oxytalan fibres are identified histochemically by the fact that they stain with aldehyde fuchsin only when tissue sections have been previously exposed to a strong oxidising agent.^{11,12} (Caroat, active component potassium peroxymonosulphate, was obtained from Degussa Ltd, Cheadle Hulme, Cheshire.)

Gomori's silver impregnation method for reticular fibres.

Gomori's one step trichrome for collagen.

McManus periodic acid Schiff sequence.

TRANSMISSION ELECTRON MICROSCOPY

One of the two nodules on the posterior cornea of case 2 was excised from the wax block, dewaxed, rehydrated, and postfixed in 1% osmium tetroxide in Palade buffer at pH 7.4. The specimen was subsequently processed and embedded in Araldite. Thin sections were stained by alcoholic uranyl acetate and lead citrate and studied under a Joel 100C electron microscope.

Results

CASE 1

The most significant abnormality was the presence of a giant dome-shaped nodule on the posterior surface of the central cornea. It measured approximately 0.4×0.19 mm in cross section. The central cornea also showed signs of previous perforating injury, such as deficiencies of Bowman's zone, disorganisation of the stromal lamellae, and fragmentation of Descemet's membrane. The basal or stromal aspect of the nodule was seen to be composed of fibrous scar tissue which had penetrated through the break in Descemet's membrane. The 'new Descemet's membrane' which covered the scar tissue and constituted the giant nodule was greatly thickened, in contrast to the old Descemet's membrane with which it was continuous. A few small guttate excrescences or warts were seen immediately to one side of the nodule.

Many oxytalan fibres were identified within the posterior or outer layers of the thickened Descemet's membrane/nodule. These fibres outlined several buried and hence unsuspected warts within the nodule in addition to those previously observed. Where oxytalan fibres penetrated between individual warts they imparted a fern leaf pattern to the nodule. Oxytalan fibres as well as presenting as distinct fibres were also seen as dots. This appearance was interpreted

ted as being fibres cut in cross section and hence encircling the warts in the nodule. Oxytalan was not observed in the more anterior or inner layers of the nodule. A relatively small number of oxytalan fibres were seen immediately beneath the endothelium over most of Descemet's membrane. A few very fine oxytalan fibres were present beneath the basal cells of the central corneal epithelium and superficial stroma in the region of the old perforating wound.

Elaunin and mature elastic fibres were not identified within any part of the cornea. The severed ends of the original Descemet's membrane observed within the nodule were, however, weakly stained by the Verhoeff elastic method, but not by aldehyde fuchsin—with or without preliminary oxidation.

Argyrophillic reticular fibres were shown by the

Gomori silver method to give the nodule and Descemet's membrane a multilayered appearance. Reticular fibres were present in the anterior layers of the nodule as well as within the oxytalan-containing posterior layers. As with oxytalan, some reticular fibres were considered to encircle the guttate excrescences.

CASE 2

Two large nodules were seen to project from the posterior surface of the cornea. The nodules appeared to be formed by the infolding of a greatly thickened Descemet's membrane. The centre of both nodules contained severed and spiraled fragments of the original Descemet's membrane. The two large nodules measured 0.14×0.2 mm and 0.2×0.1 mm in

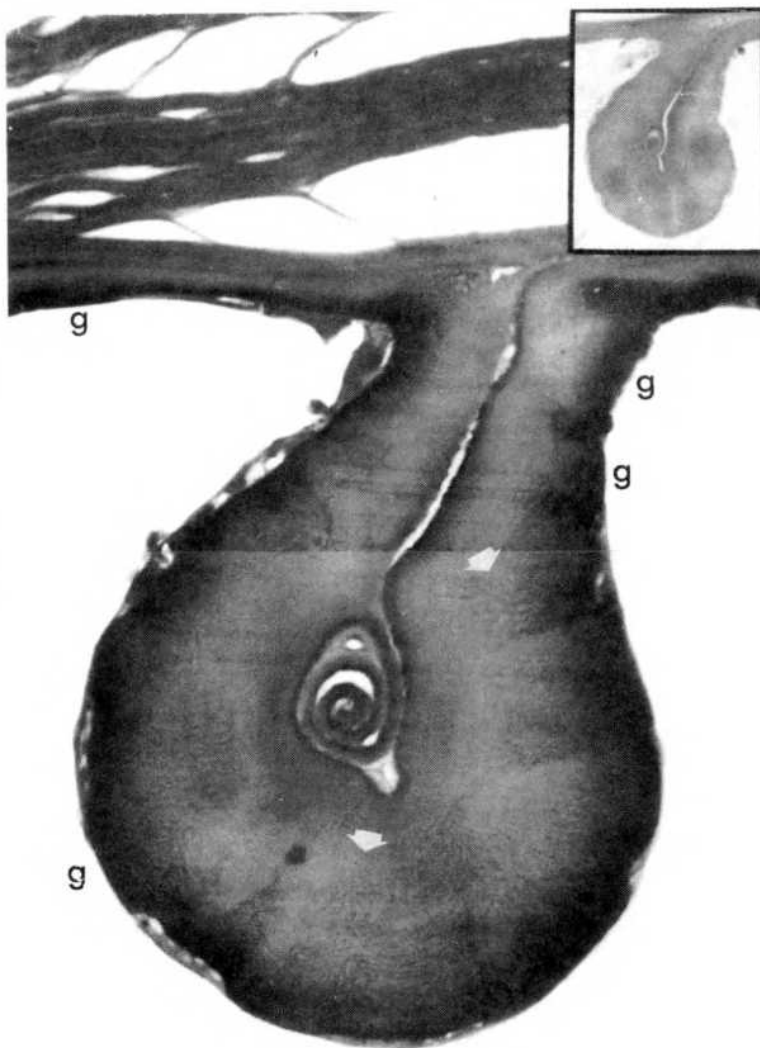


Fig. 1 One of the giant nodules from case 2. The severed and coiled Descemet's membrane is seen within the nodule. Fine oxytalan fibres (arrows) are only seen within the more posterior or outer regions of the nodule. These fibres outline unsuspected guttate excrescences (g). (Oxidation-aldehyde fuchsin, $\times 544$). Inset. If the oxidation step of the technique is omitted, oxytalan fibres fail to stain. Elaunin and elastic fibres are not present. (Aldehyde fuchsin, $\times 136$).

cross section. The posterior surface of Descemet's membrane on either side of the nodules had occasional small focal swellings or guttate excrescences.

A great many fine oxytalan fibres were identified within the more posterior-outer layers of the thickened Descemet's membrane which constituted the giant nodules (Figs. 1 and 2). The oxytalan fibre staining outlined and so revealed numerous buried individual and multiple unsuspected guttate warts within the nodules. The excrescences of Descemet's membrane proper were also outlined by oxytalan fibres. Oxytalan fibres were not present within the anterior-inner layers of the nodules. A small number of very fine fibres were demonstrated beneath the corneal epithelium and within the superficial stroma.

Elaunin and elastic fibres were not seen within the cornea. However, as with case 1, the coiled, severed ends of Descemet's membrane within the nodules were weakly stained by the Verhoeff technique but not by the aldehyde fuchsin methods.

Argyrophilic reticular fibre staining gave a multi-laminar appearance to both the normal Descemet's membrane and the nodules.

Transmission electron microscopy of the giant nodule shown in Fig. 1 revealed four morphologically different layers or zones. The first two layers, at the centre of the nodule, were formed from the anterior banded and posterior non-banded zones of the coiled, severed ends of Descemet's membrane. The third layer, which formed the bulk of the nodule and the buried excrescences, resembled the banded zone of Descemet's membrane proper. In addition it contained fine fibrils and basement membrane or ground substance material. This latter material cor-

responds to the reticular fibres seen by light microscopy. The fourth and outermost layer (Fig. 3) appeared less compact than the others and was of variable thickness. It was seen to fill the spaces between and around the individual excrescences to give a smooth outline to the nodule. This loose fibrous layer consisted of collagen fibrils, reticular fibres, and bundles of 12 nm diameter microtubules characteristic of oxytalan. Oxytalan fibres were not observed in the other zones of the nodule. The absence of elaunin and elastic fibres was confirmed.

Discussion

Oxytalan fibres have been identified in several conditions of the cornea associated with thickening of Descemet's membrane.¹⁶⁻¹⁸ In congenital hereditary endothelial dystrophy Descemet's membrane is uniformly thickened by the production of a fibrillar collagenous layer posterior to the membrane proper.²⁰ In addition to possessing collagen and basement membrane material the layer shows a great many randomly orientated oxytalan fibres.¹⁶ Likewise Descemet's membrane of the central cornea may be thickened in cases of advanced keratoconus. The retrocorneal fibrous membrane shows many roughly parallel oxytalan fibres lying at approximately 80° to the posterior surface of Descemet's membrane.¹⁸ In posterior polymorphous dystrophy the abnormal posterior fibrous layers form discrete fusiform nodular swellings.²⁰ Oxytalan fibres are present within this tissue and are seen to outline the posterior surfaces of the swellings.¹⁶ They are not apparent within the nodules or elsewhere in

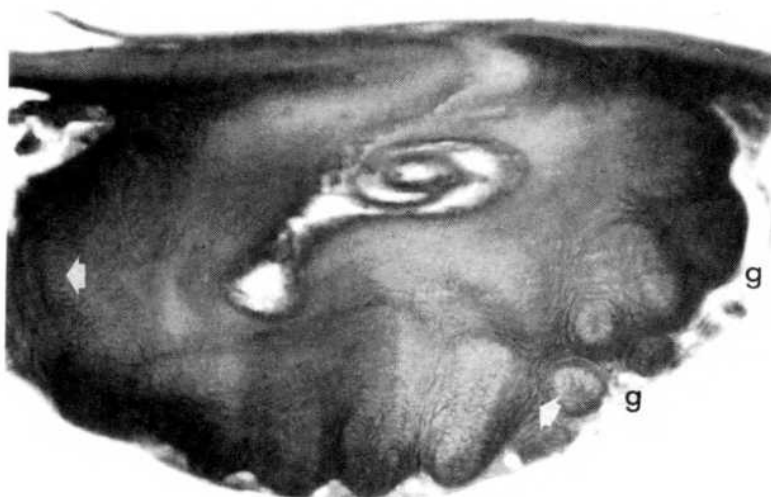


Fig. 2 The other giant nodule from case 2. Oxytalan fibres (arrows) reveal multiple guttae (g) within the outer aspects of the nodule. (Oxidation-aldehyde fuchsin, $\times 436$).

Descemet's membrane.¹⁶ Certain disease states, most notably Fuchs's endothelial dystrophy, show many dome or mushroom shaped guttate excrescences along the posterior surface of a thickened Descemet's membrane.^{5,20} Iwamoto and DeVoe²¹ showed that the thickened membrane consisted of up to five different collagenous layers: the anterior banded and

posterior non-banded zones of Descemet's membrane; a posterior banded layer which also formed the warts; a border region containing 'thin fibrils' in addition to wide-spacing collagen, collagen fibrils, and basement membrane material; and a fibrillar layer similar to the border layer but which did not show wide-spacing collagen. Oxytalan fibres are

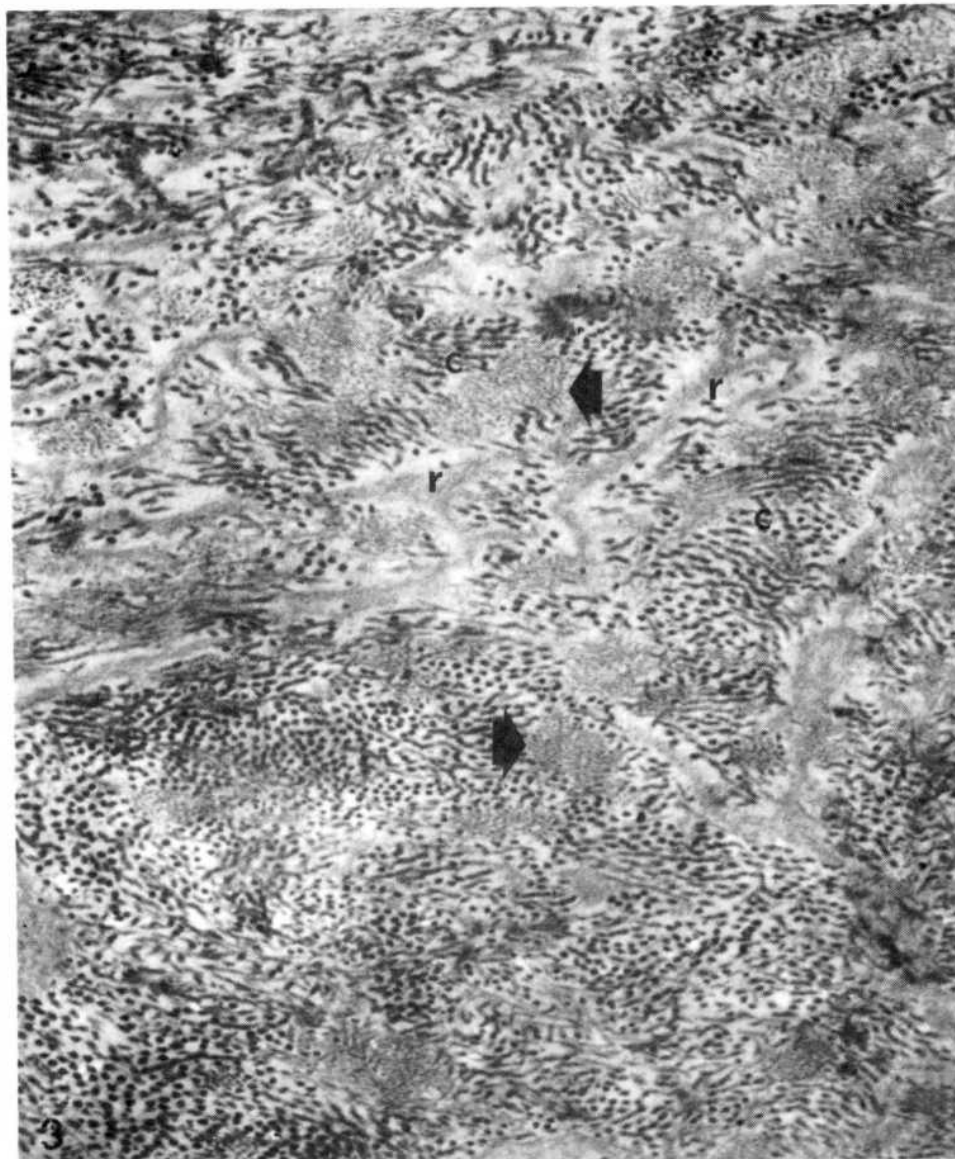


Fig. 3 Electron micrograph showing part of the loose fibrous outermost layer of the nodule shown in Fig. 1. Numerous oxytalan fibres (arrows), composed of aligned 12 nm diameter fibrils are seen. Some of these 'islands' of oxytalan probably represent successive sightings of the same long fibre. Small diameter collagen fibrils (c) are mainly shown as cross-sectioned 'dots'. Basement membrane or reticular fibres (r) are also present. (Uranyl acetate-lead citrate, $\times 37\,500$).

present in large amounts within both the border and fibrillar layers of the retrocorneal collagenous membrane.^{16,17} Oxytalan thus outlined the warts but was not present within them. Significant numbers of oxytalan fibres lay parallel to the surface of Descemet's membrane, where they encircled individual excrescences.¹⁷ Reticular fibres (basement membrane material) were present within the posterior banded layer as well as the two layers containing oxytalan fibres.¹⁷ Similar warts commonly occur in small numbers on the peripheral cornea (Hassal-Henle bodies) or over the central cornea as a part of normal endothelial aging.¹⁴ Oxytalan fibres are present in small numbers over the posterior surface only of most Hassal-Henle warts.⁷

If the giant nodules of our study could be unfolded and flattened, then on ultrastructural morphology and oxytalan fibre staining they would most closely resemble the posterior structures of Fuchs's endothelial dystrophy. However, case 1, a 60-year-old, did not have guttate excrescences on the central cornea unassociated with the nodule. Case 2, a 26-year-old, did have a small number of warts scattered over Descemet's membrane and therefore could conceivably be an early example of Fuchs's dystrophy. It is interesting that the nodules of both cases should contain increased numbers of excrescences as compared with the rest of Descemet's membrane.

To the best of our knowledge this report is the first detailed documentation of the fibrous tissue nature of giant nodules of Descemet's membrane. There was no sex or age predilection, but both patients had a history of corneal injury resulting in a transient lowering of intraocular pressure. Since wrinkles and folds in Descemet's membrane are constant features of ocular hypotony,^{22,23} it is conceivable that such folds may have developed in the cases under discussion. These folds may have been maintained for a considerable time, resulting in altered endothelial activity and overproduction of connective tissues, thus forming the giant nodules.

Multilaminar thickenings of Descemet's membrane, secondary focal guttae, and retrocorneal hyaline ridges have been observed in patients with interstitial keratitis,²⁰ and scrolls of Descemet's membrane forming giant nodules have been reported in one case.⁶ Neither of our cases had clinical or histological evidence of interstitial keratitis, and therefore such giant nodules of Descemet's membrane do not appear to be pathognomonic of interstitial keratitis.

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Corneal hypoaesthesia in asymptomatic familial distichiasis

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SUMMARY A 3-year-old child, his mother, and his uncle were found to have asymptomatic distichiasis accompanied by corneal hypoaesthesia. Slit-lamp examination of the mother and her brother revealed normal corneas, but bilateral punctate epithelial staining was found in the child. In addition the child suffered from corneal erosion in his left eye due to decreased tear secretion after left occipital craniotomy and C1 laminectomy.

Distichiasis is an extremely rare congenital anomaly in which an accessory row of eyelashes occurs along the posterior border of the lid margin in the position of the meibomian glands.¹⁻³ A strong hereditary factor has been noted in many reports,⁴⁻⁸ and the condition is apparently a dominant hereditary characteristic, since transmission is direct without sex predilection.⁹ Sometimes distichiasis is accompanied by other congenital anomalies, and in rare cases congenital ectropion, entropion, ptosis, and maxillo-facial dysostosis occur simultaneously.¹⁻⁷ Ocular irritation is not so common as one would think,¹⁻³ a fact which is probably due to the shortness and thinness (lanugo-like) of these accessory lashes. However, distichiasis may sometimes cause great discomfort and require surgical treatment.¹⁴ We describe three family members with distichiasis who were completely asymptomatic; corneal hypoaesthesia was found in each of them. This hypoaesthesia, in addition to the quality of the aberrant eyelashes, most probably contributed to the absence of any irritation. We wonder whether this hypoaesthesia is secondary to the adaptation of the corneal sensory nerve endings, to the chronic mild epithelial trauma caused by the aberrant eyelashes, or to a congenital anomaly accompanying the distichiasis.

Case report

A 3-year-old boy was referred to our department

owing to blurring of vision of his left eye three weeks after left suboccipital craniotomy and C1 laminectomy had been performed for a cerebellar mixed glioma occupying the whole posterior fossa. Examination of each eye revealed distichiasis of the upper and lower lids of both sides. The accessory cilia on the posterior margin were much thinner and lighter in colour than those on the anterior margin of the lid borders. Some were so light and thin as to be seen only with the slit-lamp. There were 10 aberrant cilia in the right upper lid and 12 in the right lower lid; 12 aberrant cilia were found in the left upper lid and 15 in the left lower lid. All the cilia pointed backwards and impinged on the eyeball. Both corneas showed punctate epithelial staining in their inferior half. In addition a large epithelial erosion was found in the paracentral area of the left cornea. No other abnormal findings were seen in the anterior and posterior segments. Corneal sensitivity testing by the corneal aesthesiometer disclosed very low values (1.5 units in both eyes). Schirmer test values were found to be above 15 mm in the right eye and below 10 mm in the left. The corneal erosion was treated by lateral tarsorrhaphy combined with local treatment with chloramphenicol ointment (5%) four times daily.

After two weeks the corneal erosion healed completely but epithelial staining still remained in both eyes. Therefore electroepilation of the accessory eyelashes was performed, after which procedure the punctate staining disappeared almost completely. As the Schirmer test results were found to be improved (above 10 mm) in the left eye, the lateral tarsorrhaphy was opened and the local treatment stopped. On follow-up examinations the aberrant eyelashes

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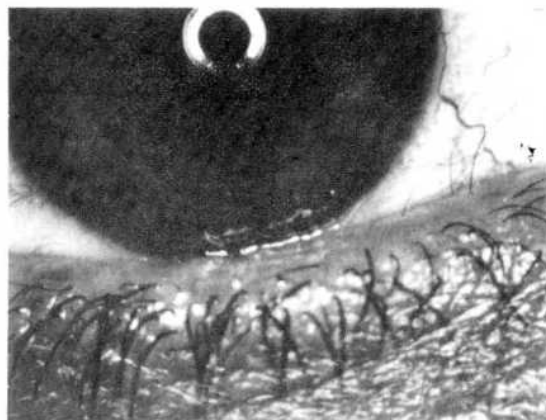


Fig. 1 Distichiasis in upper lid of the mother's right eye.



Fig. 2 Distichiasis in upper lid of mother's left eye.

reappeared and the child was completely asymptomatic, but very mild punctate staining was still noticed in the lower part of both corneas. It was decided to keep the child on artificial tears treatment six times daily in both eyes.

We checked the child's family members and found that his mother and her brother, 30 years and 23 years old respectively, also had distichiasis in both eyelid margins, but without corneal lesions (Figs 1, 2). The mother's brother had no children and the child had no siblings. No other family members were found to have distichiasis, and their general physical and ophthalmological examination revealed no abnormal findings.

Discussion

In distichiasis the aberrant lashes are usually small and very soft and fine, showing little pigmentation, but they may at times be as fully developed as the outer row.^{1,2} Anatomical investigation has verified that they replace the meibomian glands, which become modified and take on hair-bearing functions.⁸⁻¹¹ Sometimes these glands appear to lose all their usual characteristics, being entirely replaced by the follicles of cilia into which sebaceous glands open, but at other times some typical meibomian acini remain while opening into the follicles of the anomalous cilia like normal sebaceous glands.¹⁰⁻¹³ Begle¹⁰ suggested that this condition might be atavistic, as it is common in animals. Hereditary cases have been reported by several authors, mainly in the older literature.³⁻⁷ As has been mentioned, the condition is usually transmitted as a dominant characteristic.⁵ Pico⁵ has described a family with 10 individuals who had distichiasis, eight of whom had associated ectropion and the other two distichiasis as an isolated anomaly.⁵ Other congenital anomalies

have been described as being found together with distichiasis.^{4,6,7}

The clinical importance of distichiasis lies in the irritation caused to the cornea,^{1-3,5} but as was found in the family reported here and in some others mentioned in the literature the irritation is usually less than might be expected; often this anomaly is completely asymptomatic owing to the fineness of the eyelashes¹⁻³ and probably, we assume, to corneal hypoaesthesia or to adaptation by the corneal nerve endings—a hypothesis difficult to prove. Fox² described a case of distichiasis accompanied by slight corneal hypoaesthesia, but others have not mentioned this interesting fact in the relatively few reports written on this subject in recent years.³⁻⁷ If the irritation is mild and the abnormal eyelashes are few, electroepilation may solve the problem, but, if a complete row is present and the irritation is severe enough, a plastic operation for trichiasis is indicated.^{1,14} In the family described here two brothers and their sister were asymptomatic, the child of the last having distichiasis with corneal complications due to deficiency of tearing reflex. It is interesting to note that all of them were found to have corneal hypoaesthesia when tested with the corneal aesthesiometer.

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Bipalpebral sliding flap in the repair of inner or outer canthal defects

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SUMMARY Seven patients were successfully treated with a bipalpebral sliding flap for the repair of medial or lateral canthal defects. In our experience this technique minimises the size of the associated surgical repair—a skin graft for the inner canthus or a cheek rotation flap for the outer canthus.

The bipalpebral flap (BPF) consists of two cutaneous flaps—a sliding flap from the lower lid and a rotating flap from the upper lid. These skin flaps are dissected from the orbicularis muscle with careful coagulation of all tiny bleeding vessels. Skin flaps were preferred to myocutaneous flaps because they allow a simpler surgical procedure.

The principal advantage of this technique is that it minimises the size of the associated repair, decreases the size of the skin graft in large defects, and uses adjacent skin of similar appearance and thickness to that lost from the defect.

We report our experience with the BPF, an under-used but effective technique to repair medial or lateral canthal defects, using both upper and lower lid skin. We believe the BPF was first reported on by Brun and Morax¹ in 1899, but since that time the technique has been forgotten.

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Patients and methods

Seven patients underwent surgery for medial or lateral canthal lesions. In six cases the lesion consisted of a basal cell carcinoma which was excised with frozen section control; the remaining case was of lentigo maligna. Five cases had medial canthal defects and two had lateral canthal defects.

A BPF operation was performed in all cases, and the flap was sufficiently large completely to cover the defect in two cases. In two other cases with medial defects a skin graft was required in addition to the BPF. A glabellar flap and a skin graft in addition to the BPF were required to cover a large medial defect in one case.

Details of these cases are summarised in Table 1.

SURGICAL TECHNIQUE

As illustrated in Figs. 1 and 2 (medial canthal and lateral canthal defects respectively), the BPF consists

Table 1 Clinical data and summary of the results

Case	Age	Localization	Surgery bipalpebral flap (BPF)	Histological data	Frozen section control	Previous treatment	Cosmetic results	Follow-up (months)
1	76	OA	BPF + sliding flap	Lentigo maligna	No		Good, slight ectropion	4
2	86	OA	BPF + sliding flap	BCC	Yes, CE		Good	6
3	82	IA	BPF + skin graft	BCC	Yes, CE		Good	16
4	65	IA	BPF + skin graft	BCC	Yes, CE		Good	12
5	66	IA	Full thickness lid graft + glabellar flap + BPF	BCC	Yes, CE	Radiotherapy	Moderate	22
6	63	IA	BPF	BCC	Yes, CE		Good	3
7	63	IA	BPF	BCC	Yes, CE	Surgery	Good	2

BCC=basal cell carcinoma CE=complete excision IA=inner canthus. OA=outer canthus

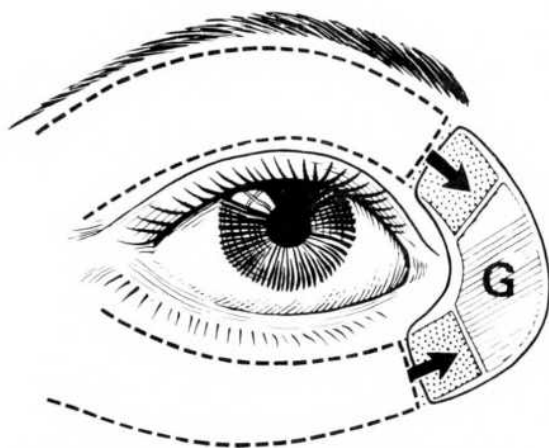


Fig. 1 Bipalpebral sliding flap associated with a skin graft for the closure of a medial defect.

of two cutaneous flaps. The skin is dissected from the orbicularis muscle with scissors, and the tiny bleeding vessels are carefully coagulated. The upper lid incisions for both inner and outer canthal defects are made 2 mm above the cilia and 2 mm below the eyebrow. For outer defects the lower lid incisions consist of a horizontal incision 2 mm below the cilia and a curved incision starting from the lower part of the defect to the inner portion of the cheek. For an

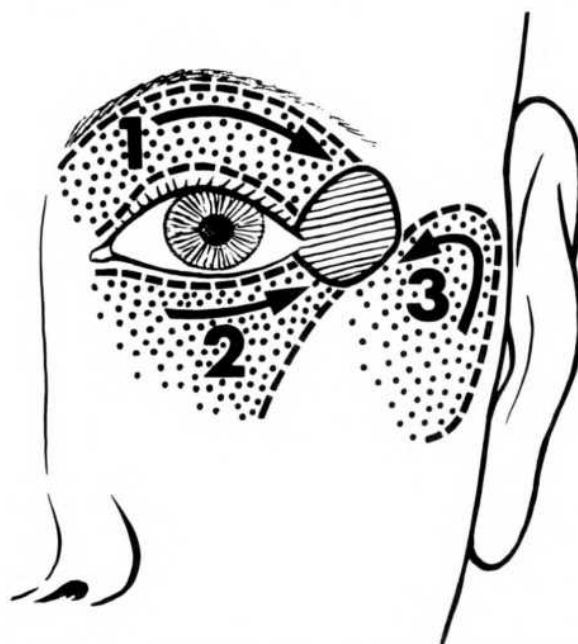


Fig. 2 Bipalpebral sliding flap associated with a large cheek rotation flap for a large lateral defect.

inner defect the upper incision of the lower lid starts 2 mm below the cilia at the outer angle. A parallel incision is made 10 to 20 mm beneath this incision.

Flaps are sutured with 6-0 Prolene without a local pressure bandage in most cases. However, POR-8 (Sandoz) was used to decrease the bleeding. When a skin graft is necessary, additional 5-0 Prolene sutures are placed through the skin in the middle part of the graft for fixation to the orbicularis muscle or to the periosteum.

After resection of the lacrimal portion of the eyelid in the inner angle, the tarsi are reattached to a wire fixed to the anterior lacrimal osseus crest.

Frozen section control was used in six cases. Small pieces of skin were excised all round the main defect as well as tissue underlying the tumour for examination as described by Chalfin and Putterman² and Adenis *et al.*³

Results

Seven patients were treated successfully with a BPF to help close medial and lateral canthal defects. The cosmetic results were good in all cases except case 5, with only a moderately satisfactory cosmetic result. Cases 1 and 2 had moderate lower eyelid ectropion which disappeared in six months. In case 6, moderate epiphora remained but did not require another surgical procedure. No patient had ptosis before or after treatment.

The excision of basal cell carcinoma in all six cases was performed under frozen section control. This technique enabled us to excise the tumour completely in all cases. The average follow-up was 10 months in these six cases, but since the maximum follow-up period was only 22 months there has not been sufficient time to exclude absolutely any future recurrence of these tumours.

Discussion

Different techniques have been used in the surgical repair of the angles of the eye.

Medial canthal defect: (a) The 'laissez-faire' first described by Fox and Beard.⁴ (b) The full thickness skin graft, which is used by a large number of authors listed in a recent paper.³ (c) The tarsoconjunctival flap from the upper eyelid.⁵ (d) A V-Y glabellar flap or a midline forehead flap, as recommended by Collin.⁶ (e) A free tarsoconjunctival graft from the upper eyelid combined with a nasal pedicle skin-muscle flap, as described by Leone and Hand.⁷

Lateral canthal defects: (a) Direct closure with adequate undermining of the surrounding eyelid skin. The cut edges of the tarsal plates can be sutured to the orbital rim. 8-10 (b) Full thickness skin grafts

have been used by Mustarde¹¹ and Fox¹² for moderate defects but are not very suitable for large outer canthal defects because of the difference in skin thickness. (c) A cheek rotation flap described by Mustarde¹¹ can provide a large amount of skin in the inferior portion of the angle. (d) The forehead flap of Fricke from above the eyebrow. (e) A tarsoconjunctival flap from the upper eyelid.⁵ This technique is recommended by Mac Cord,⁸ Soll,¹³ and Putterman.¹⁴

ADVANTAGES OF THE BPF

All these techniques except skin grafting are difficult to use in cases of large canthal defects. With large skin grafts poor results are frequently encountered after radiotherapy. The BPF is very useful in covering these extensive defects and/or minimising the amount of skin graft needed, particularly in treating recurrences following radiotherapy. Another advantage of the BPF is to cover the canthal defect with skin which is of similar thickness and color. If histological control is positive, this repair can more easily accommodate the larger defect following excision. The principal value of the technique, however, is to minimise the size of the associated repair—a skin graft or a cheek rotation flap.

CONCLUSION

The operation of bipalpebral sliding flap is a useful technique in repairing inner or outer angle defects when associated with another flap or with a skin graft. It minimises the size of the associated repair and is cosmetically acceptable.

We thank JRO Collin for reading the paper, his advice, and stimulating discussion.

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Intraocular acyclovir levels after subconjunctival and topical administration

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SUMMARY Substantial levels of acyclovir were detected in the aqueous and vitreous of New Zealand rabbits at various time intervals following subconjunctival injection. Intravitreal penetration of acyclovir after topical application was poor.

Acyclovir is an antiviral agent that possesses substantial activity and specificity against most members of the herpes simplex virus family with the possible exception of cytomegalovirus.¹ Acyclovir shows little toxicity toward uninfected human cells.² This preliminary study was designed to evaluate the intraocular levels of the drug at different time intervals following subconjunctival injection and topical administration. To the best of our knowledge no other report describes intraocular penetration of acyclovir following subconjunctival administration or vitreous levels after topical application of acyclovir.

Materials and methods

A total of 47 New Zealand white rabbits, weighing approximately 2 kg each, were divided into three groups for this study.

Part A. The animals were anaesthetised with an intravenous injection of ketamine hydrochloride. A single 25 mg injection of acyclovir sodium (0.5 ml of a 50 mg/ml (50 g/l) solution) was given under the bulbar conjunctiva of one eye of each rabbit. At 1, 3, 5, and 24 hours after subconjunctival injection aqueous and vitreous samples were removed and immediately refrigerated at -27°C. Each sample of aqueous was obtained with a 30-gauge needle inserted through clear cornea. Vitreous samples were aspirated with a 23-gauge needle placed 2 mm behind the limbus. Levels of acyclovir were determined by radioimmunoassay.³

Part B. The experiment was repeated with a 2.5 mg injection of acyclovir (0.5 ml of a 5 mg/ml (5 g/l)

solution) under the bulbar conjunctiva of one eye of each rabbit. Aqueous (0.1 ml) and vitreous (0.1 ml) samples were obtained in the same fashion as in part A at 0.5, 1, 2, 3, and 22 hours after subconjunctival injection.

Part C. One eye from each of 10 rabbits was treated with 3% acyclovir ointment. A 1 cm ribbon of the ointment was placed in the inferior cul de sac of each eye every five hours for 25 hours. A total of six applications were given to each eye. At 1, 2, and 3 hours after the last application of acyclovir vitreous samples were obtained and immediately refrigerated at -27°C. Acyclovir levels were determined by radioimmunoassay.

Results

Part A. Clinically the rabbits showed crystallisation of acyclovir after subconjunctival injection. The crystals dissolved within 18 hours. Minimal conjunctival reaction followed the injection. Relatively high aqueous (Table 1) and vitreous (Table 2) levels of acyclovir were detected after subconjunctival injection.

Part B. Subconjunctival crystallisation of acyclovir was not detected in this group. Substantial aqueous (Table 3) and vitreous (Table 4) levels of acyclovir were obtained.

Part C. Vitreous levels following topical application of the drug were negligible (Table 5).

Discussion

Acyclovir, 9-(2-hydroxyethoxymethyl)guanine, is also called acycloguanosine.^{4,5} In-vitro acyclovir is

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Table 1 *Acyclovir levels in rabbit aqueous humour*

Time (h)	Sample	Aqueous humour samples	
		Concentration	
		$\mu\text{g/ml}$	μM
1-0	A1	258.84	1150.38
	A2	533.13	2369.43
	A3	137.83	612.59
3-0	A4	104.42	464.07
	A5	297.42	1321.86
	A6	199.32	885.87
5-0	A7	71.50	316.23
	A8	102.49	455.50
	A9	82.55	366.88
24-0	A10	2.08	9.25
	A11	3.43	15.24
	A12	1.72	7.62

Samples were obtained after rabbits received a subconjunctival injection of 25 mg (0.5 ml) of acyclovir sodium salt.

Table 2 *Acyclovir levels in rabbit vitreous humour*

Time (h)	Sample	Vitreous humour samples	
		Concentration	
		$\mu\text{g/ml}$	μM
1-0	V1	2.31	10.27
	V2	4.73	21.03
3-0	V3	1.61	7.17
	V4	23.02	102.30
	V5	34.79	154.62
5-0	V6	65.95	293.09
	V7	15.44	68.62
	V8	32.58	144.78
24-0	V9	0.21	0.95
	V10	0.13	0.57
	V11	0.22	0.99
	V12	0.31	1.32

Samples were obtained after rabbits received a subconjunctival injection of 25 mg (0.5 ml) of acyclovir sodium salt.

active against DNA viruses of the herpes group.⁴⁶ Because acyclovir is activated in vivo only by virus-specific enzymes, it is non-toxic to uninfected cells.²

In-vitro acyclovir has been found to be effective against several members of the herpes virus family. Minimum inhibitory concentrations (MIC) of acyclovir have been reported as 0.2, 0.4, 1.0, 1.5, and 16.3 $\mu\text{g/ml}$ (mg/l) for herpes simplex virus type I (HSV-I), herpes simplex virus type II (HSV-II), varicella zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) respectively.⁴ The ID₅₀ (50% inhibitory dose) in herpes virus isolated from human infections was 0.15 SD 0.09 μM , 1.62 SD 0.76 μM , and 3.75 SD 1.30 μM for HSV I, HSV II, and VZV. Two CMV isolates had ID₅₀s of 100 and 160 μM , while four other isolates showed no plaque reduction at 200 μM .²

Table 3 *Acyclovir levels in rabbit aqueous humour*

Time (h)	Sample	Aqueous humour samples	
		Concentration	
		$\mu\text{g/ml}$	μM
0-5	A1	1.13	5.04
	A2	2.98	13.20
	A3	>45.00	>200.00
1-0	A4	>45.00	>200.00
	A5	16.00	71.10
	A6	9.36	41.60
2-0	A7	4.04	17.90
	A8	7.87	35.00
	A9	9.41	41.80
3-0	A10	3.27	14.50
	A11	5.59	24.90
	A12	9.19	40.09
22-0	A13	<0.56	<2.50
	A14	<0.56	<2.50

Samples were obtained after rabbits received a subconjunctival injection of 2.5 mg (0.5 ml) acyclovir.

Table 4 *Acyclovir levels in rabbit vitreous humour*

Time (h)	Sample	Vitreous humour samples	
		Concentration	
		$\mu\text{g/ml}$	μM
0-5	V1	6.28	27.90
	V2	0.90	3.98
	V3	0.62	2.76
1-0	V4	0.95	4.23
	V5	1.17	5.21
	V6	2.70	12.00
2-0	V7	1.43	6.36
	V8	<0.56	<2.50
	V9	1.30	5.78
3-0	V10	1.88	8.39
	V11	1.36	6.06
	V12	0.92	4.09
22-0	V13	<0.56	<2.50
	V14	<0.56	<2.50

Samples were obtained after rabbits received a subconjunctival injection of 2.5 mg (0.5 ml) acyclovir.

Topical application of acyclovir resulted in vitreous levels well below the therapeutic range for members of the HSV family. Subconjunctival injection with 25 mg of the sodium salt of acyclovir produced, in most instances, aqueous and vitreous levels sufficient to inhibit members of the HSV family with the possible exception of CMV. The vitreous acyclovir levels remained in therapeutic proportions for at least three hours after injection. Therapeutic aqueous levels for HSV I and HSV II were present at 18 hours after injection, but vitreous levels were subtherapeutic for all members of the HSV family except HSV I. The variation in acyclovir levels probably resulted in part from an uneven absorption

Table 5 Acyclovir levels in rabbit vitreous humour

Time (h)	Sample	Vitreous humour samples	
		Concentration	
		$\mu\text{g/ml}$	μM
1-0	V1	<0.02	<0.10
	V2	<0.03	<0.10
	V3	<0.02	<0.10
2-0	V4	0.03	0.12
	V5	<0.02	<0.10
	V6	0.02	0.10
3-0	V7	<0.02	<0.10
	V8	0.04	0.18
	V9	<0.02	<0.10
	V10	0.02	0.10

Samples were obtained after rabbits received a topically applied 1 cm ribbon of 3% acyclovir every five hours for a total of six applications over a 25-hour period

due to crystallisation from the subconjunctival injection. This occurred only with the higher dose of acyclovir.

The second part of the experiment (subconjunctival injection of 2.5 mg of acyclovir) produced aqueous levels in excess of the MIC for all members of the HSV family except CMV for at least three hours after injection. Negligible levels of acyclovir were detectable 22 hours after injection. Vitreous levels were therapeutic for HSV I, HSV II, VZV, and EBV, but not CMV during the first three hours after injection.

Patients with herpes simplex retinitis have had substantial visual loss and retinal damage.⁷⁻¹¹ A recent communication¹² has suggested an association between acute retinal necrosis and HSV infection. HSV has been demonstrated in the anterior chamber in iritis, keratouveitis, and disciform corneal oedema with associated iritis.¹³⁻¹⁵ Herpes virus particles also have been detected in an iridectomy specimen removed from a patient with herpetic uveitis, deep keratitis, and secondary glaucoma.¹⁶ Our findings indicate that subconjunctival injection of acyclovir may provide effective drug levels for the primary or adjunctive treatment of deep herpetic disease such as retinitis, keratouveitis, iritis, and possibly acute retinal necrosis. Caution must be exercised, how-

ever, in making recommendations based on data obtained only from rabbit eyes. Subconjunctival acyclovir infection should avoid toxic reactions reported after parenteral administration.

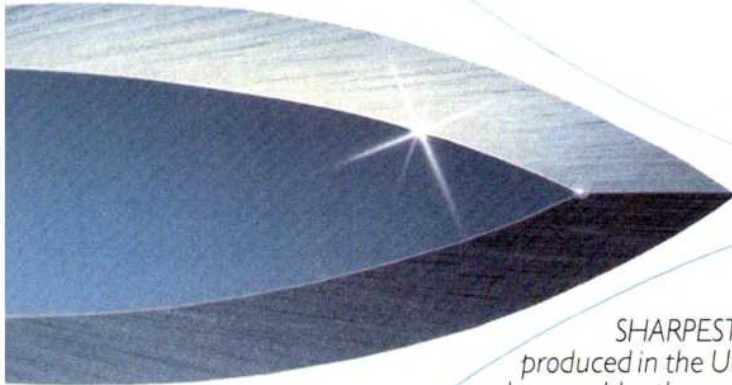
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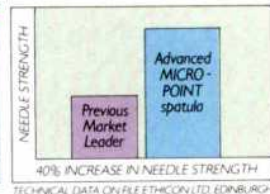
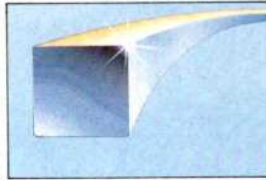
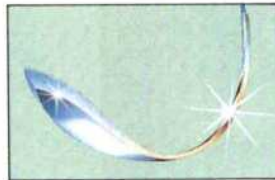
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Visual changes mediated by beer in retrobulbar neuritis – an investigative case report

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SUMMARY A patient with established retrobulbar neuritis and Uhthoff's phenomenon who claimed that his visual acuity improved after drinking beer was assessed by detailed quantitative psychophysical tests. Studies of electrophysiological responses and biochemical levels of blood serum before and after drinking on several occasions were also made. The results of tests of contrast sensitivity, spectral sensitivity, flicker sensitivity, and visually evoked potential confirmed his observation. Some mechanisms for this phenomenon are considered.

Since its description by Uhthoff in 1890¹ the exacerbation of symptoms in patients with demyelinating disease, associated with increase in body temperature, has been reported frequently in the clinical literature.² In vitro, drastic effects on the conduction of partially demyelinated axons have been demonstrated following slight changes in temperature and extracellular fluid composition.³ In vivo, however, the relevance of such variations is less well understood.

The visual pathway, especially the optic nerve and optic chiasm, is particularly sensitive in multiple sclerosis (MS).⁴ The electrophysiological and psychophysical investigation of visual parameters is effective in the detection of clinically 'silent' lesions⁵ and is helpful in the understanding of the underlying pathophysiology in demyelinating disease.⁶ Carefully standardised and comprehensive measurement of visual performance is used here to evaluate the claimed improvement in visual symptoms after drinking beer. This method of achieving a remission has not been reported previously, and seems to be a type of 'reversed' Uhthoff's phenomenon.

Patients and methods

PATIENT

The patient, a 40-year-old joiner, suffered an episode of retrobulbar neuritis (RBN) in 1976 affecting his right eye, after which his visual acuity recovered. In

1977 a second episode in the same eye reduced his visual acuity to counting fingers (CF). The left eye was also involved by RBN in 1981 and again in April 1982. In September 1982 examination showed the cerebrospinal fluid to be normal. On both the last occasions of an attack of RBN ACTH treatment was given. Other than Uhthoff's sign there are no other indications of demyelinating disease.

Examination of the fundus revealed a pale grey right disc and temporal pallor of the left disc. Owing to the difficulty in central fixation and the poor acuity in the right eye, most psychophysical tests were carried out on the less defective left eye only. The Amsler grid showed a paracentral scotoma for the left eye, though the patient has central fixation in this eye (Propper projection ophthalmoscope grid).

Visual acuity for the right eye seems stable at CF at 1 metre, regardless of environmental factors. Left visual acuity remains stable over any one day, 6/9 on a 'good' day, 6/60 on a 'bad' day, unless some specific aggravating factor is experienced, notably strenuous exercise, increased temperature or emotional stress. He finds two to three pints (1.2–1.8 l) of beer (taken once a week) always improves his visual acuity to its peak, even on a day when it is persistently low.

Methods

Methods for measuring the patient's responses are considered under the following categories: spectral sensitivity, flicker sensitivity, contrast sensitivity (for pattern and movement), visually evoked potentials, and biochemical assessment. Measurements are re-

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lated to immediately before and approximately one hour after drinking 2.25 pints (1.3 l) of beer and to an average normal response. The patient was studied for changes in visual responses with drink on six separate occasions, each beginning at 11.30 am after a 30-minute rest period.

Results

SPECTRAL SENSITIVITY

The data for spectral sensitivities were derived from the Maxwellian view apparatus described by Zisman *et al.*⁷ and Alvarez *et al.*⁴; they have been shown to be sensitive in the assessment of abnormal visual function. Thresholds were determined for a 1°, 1 Hz spectral test spot on a 1000 troland (td) white background. The subject was instructed to fixate four black fixation spots, in the centre of which appeared the test spot. The examiner controlled the test spot intensity by the method of descending limits; the subject had no feedback with regard to normal or previous performance. The average results for 19

normal eyes (± 1 SD) are shown in Fig. 1A and 1B by the solid line with error bars.

The results for the patient are shown by the filled circles and the crosses in Figs. 1A and 1B; the dashed line with crosses represents his mean spectral sensitivity before drink. Responses are seen to be depressed more than 3 log units relative to normal. The light source for the apparatus was unable to produce a high enough intensity at wavelengths shorter than 475 nm to be detected by the patient (before drink). After drinking beer at approximately 20° C (Fig. 1A, trial 1) and beer kept at 37° C (Fig. 1B, trial 4), an increase in spectral sensitivity of 1.5 log units was noted (solid line with filled circles). This remarkable overall increase in sensitivity in a period of less than two hours correlates with an improvement of the Snellen acuity to 6/9 for both trials (Table 1).

FLICKER SENSITIVITY

Temporal properties in vision are frequently reported as being disrupted in demyelinating disease.⁸⁻¹¹ The patient's flicker responses were tested monocularly

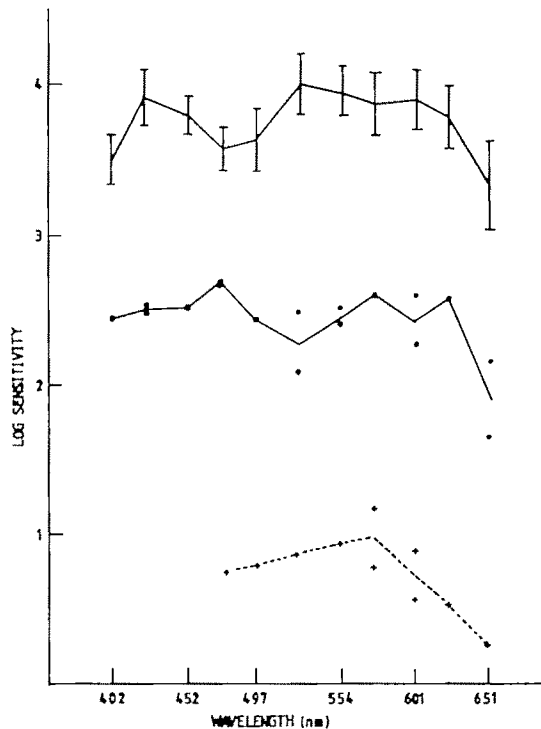


Fig. 1A

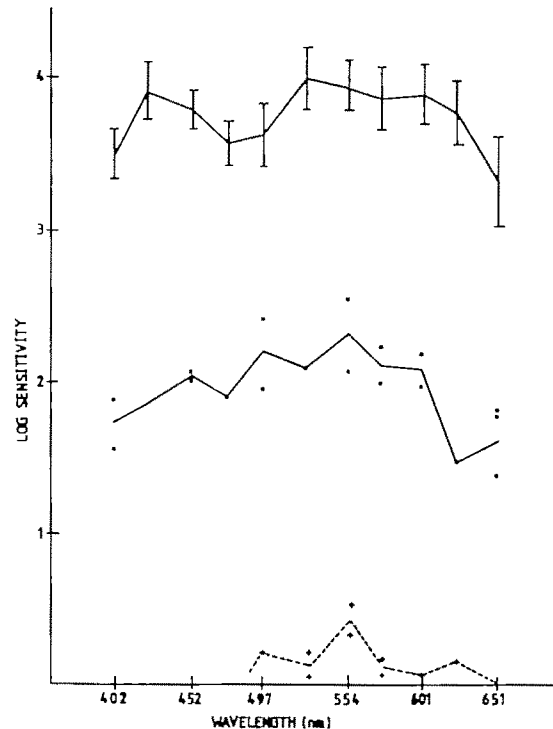


Fig. 1B

Fig. 1 Spectral sensitivity curves for 0.5 s flashes with a 1° foveal test stimulus on a 1000 td white (3200 K) background. Fig. 1A compares average normal response (solid line with error bars for 1 SD) with the patient's response before drinking (dashed line with crosses) and after drinking (solid line with filled circles) beer kept at 20° C. Fig. 1B compares average normal response (solid line with error bars for 1 SD) with the patient's response before drinking (dashed line with crosses) and after drinking (solid line with filled circles) beer kept at 37° C.

Table 1 Psychophysical and electrophysiological test results before and after drinking 2.25 pints (1.3 l) of beer kept at different temperatures

Trial	Temperature of fluid (beer)	Spectral sensitivity (log units)		Critical flicker fusion (Hz)	Contrast sensitivity resolution limit for detection in cycles/degree		VEP (peak amplitude)	VA (Snellen)
		At 525 nm	At 600 nm		Pattern	Movement		
1. A Before	20° C	0.86	0.72	8	—	—	—	6/60
B After		2.26	2.42	17	—	—	3.4	6/18
2. A	10° C	2.2	2.5	8	16.3±0.66	9.5±0.5	6.5	6/12
B		2.5	2.4	10	22.5±0.3	8.0±0.3	8.0	6/9
3. A.	37° C	2.3	2.64	8.5	20.2±0.3	8.0±0.64	7.0*	6/12
B		2.62	2.25	11	24.6±0.8	8.5±0.5	8.9	6/9+
4. A	37° C	0.12	0.06	8	16.7±0.5	9.0±0.7	—	6/36
B		2.10	2.08	11	21.8±0.8	8.0±1.1	7.5	6/9

* See Fig. 4.

by means of flicker modulation sensitivity.¹²

Measurements were made on a Telequipment D16A oscilloscope screen subtending 2 by 1.8° with a green, P31 phosphor at a luminance of 9 cd/m² (viewing distance of 285 cm). The patient was not aware of his performance, since the flicker frequency was selected randomly by the examiner and the contrast was continuously varied by the subject. The average flicker modulation sensitivity range for 20 normal eyes is shown by the error bars (±2 SD) in Fig. 2. It can be seen that the patient's response to flicker before drink (dashed line with cross, Fig. 2) was greatly depressed (only a small peak in sensitivity for flicker detection at 7 Hz). After 2.25 pints (1.3 l) of 20° C beer the flicker modulation sensitivity,

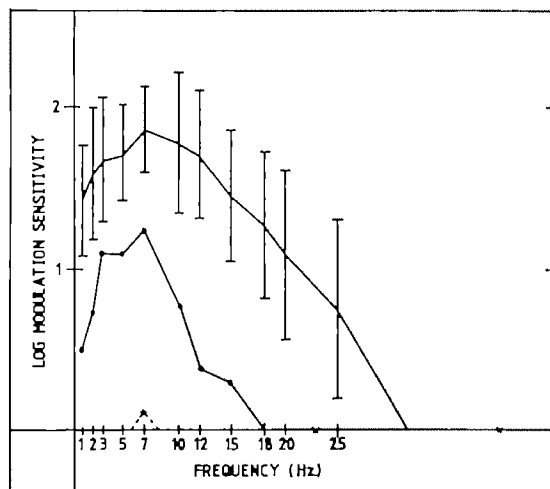


Fig. 2 Modulation sensitivity functions for monocular viewing of a 2° (horizontal) × 1.6° screen: screen luminance, 9 cd/m². Results for average normal response (solid line with error bars for 1 SD). The patient's response before drinking (dashed line with cross) and after drinking (solid line with filled circles) beer kept at 20° C.

measured within two hours, showed an improvement greater than 1 log unit (solid line with filled circles, Fig. 2).

CONTRAST SENSITIVITY-PATTERN AND MOVEMENT DETECTION

For this experiment a Tektronix 608 oscilloscope was used to generate a grating pattern; stimulus and data collection were controlled by a PDP 11-23 computer. The patient indicated when he had reached the relevant threshold by pressing a button, and four settings were obtained for each spatial frequency. Frequent rests were required, and adjacent spatial frequencies were never tested consecutively to avoid adaptation effects. The patient was again unaware of his performance, as there was no baseline from which he could judge his previous endpoint. At the viewing distance of 114 cm the stimulus subtended 5° visual angle. Screen luminance was now 46 cd/m² and the sinusoidal grating was reversed at a rate of 2 Hz.

The data from various trials (Table 1) indicate how the patient's visual sensitivity and resolution changed as a result of his drinking approximately 2.25 pints (1.3 l) of beer. The marked pattern contrast sensitivity increase across all spatial frequencies is shown in Fig. 3. A contrast threshold of 1.0 represents 100% contrast, while 0.3 is equivalent to 30% and 0.1 to 10%. The spatial resolution limit, depicted by p, increased from 17 c/deg to 23 c/deg, corresponding to an improvement in Snellen visual acuity (VA) (which was measured at each 'before' and 'after' contrast sensitivity session) of 6/18 to 6/9. A localised loss of sensitivity or a spatial frequency 'notch' was observed at approximately 7 c/deg in all trials on this apparatus with VA worse than 6/9. When the pattern was reversed in phase by 180° (at 2 Hz in this experiment; dark bars became light and light bars became dark) an illusion of movement was noted; the bars of the grating appeared to 'march' from left to right across the screen. The patient's task was to adjust the

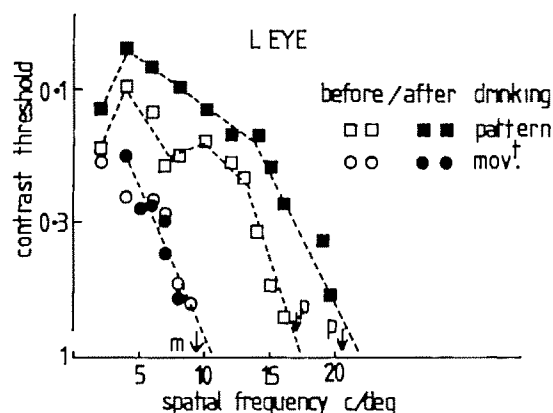


Fig. 3 Pattern and movement thresholds before (open symbols) and after (filled circles) drinking. Standard errors are within symbols. Arrows indicate resolution limits for pattern (p) and movement (m) sensitivity. A 'notch' in sensitivity is noticeable at approximately 7 c/deg. Pattern detection (including the resolution limit) shows a marked improvement after drinking, while movement detection remains unchanged.

contrast until the 'movement' just stopped. The threshold for movement was taken at five different spatial frequencies (Fig. 3). Sensitivity for movement remained constant (filled and unfilled circles, Fig. 3) regardless of fluctuations in pattern vision. The spatial resolution limit—that is, the finest gratings which allowed detection of movement—at 100% contrast also remained constant and coincided with that predicted by extrapolation—that is, equivalent to the movement threshold 'cut-off'.¹³

VISUALLY EVOKED POTENTIALS

Visually evoked potentials (VEPs) as measured in

cases of RBN often show an increase in latency and decrease in amplitude.¹⁴ VEPs were generated by contrast reversal (checkerboard pattern) from a Medelec TV pattern generator and displayed on a conventional 26 inch (66 cm) television viewed at 114 cm. The average luminance of the screen was 40 cd/m² and the contrast between squares was approximately 50%. Electrodes were placed 1 cm and 5 cm above theinion and both referenced with respect to a mid-frontal electrode. Amplifier corner frequencies were 0.3 and 70 Hz, and the Medelec system was used to average and record the VEP (128 averages).

On the two separate occasions when the VEP was recorded for this patient the P100 component showed a significant and consistent delay for all check size stimuli (Table 1), both 'before' and 'after' drinking. There was, however, a marked amplitude change 'after' drinking which was confined to the smaller check stimulus, similar to the recovery in RBN, which usually takes several weeks (Fig. 4).

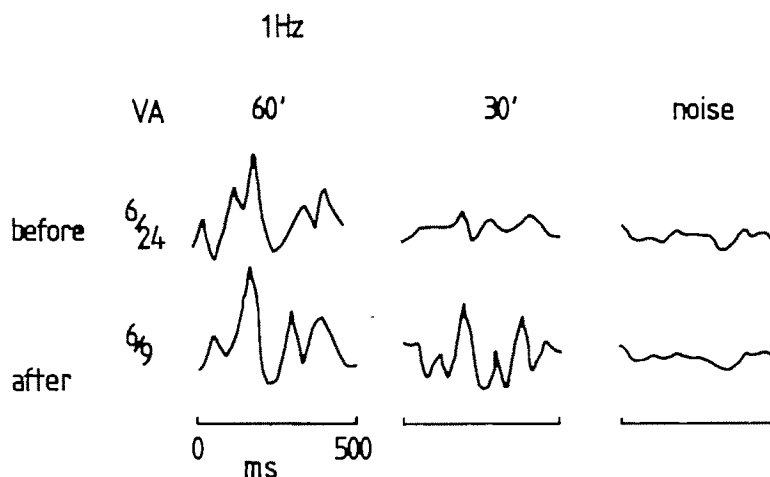
BIOCHEMICAL ASSESSMENT

The possibility of significant alteration in the serum biochemical profile mediated by drinking beer was investigated by measuring the following: urea, electrolytes, calcium, glucose, acid/base state (with venous samples), and osmolality. These parameters were measured before and again one hour after drinking on three separate occasions. No significant changes were noted.

Discussion

One or more episodes of RBN, which strongly correlate with the presence of demyelinating disease, may affect the visual performance via optic nerve

Fig. 4 Representative VEPs from the patient derived monopolarly (reference: midfrontal) from 2 cm above inion. Large checks (60') generate virtually the same VEP regardless of visual acuity (VA), whereas a large difference in amplitude ($\times 3$) is obtained with 30' checks. Latency is prolonged (146 ms) compared with the time in normal persons (100 ms) and does not change with changes in VA.



fibres in two ways: (1) a non-selective mechanism depressing responses in luminance channels (measured by deLange curves) and colour/acuity channels (measured by spectral sensitivity, VA, and contrast sensitivity); and/or (2) a specific mechanism that blocks conduction of fast impulses (measured by critical flicker fusion (CFF) and 25 Hz chromatic flicker). Each of 30 cases of RBN tested previously¹⁵ demonstrated at least two of the features of mechanism (1). Of those patients that also demonstrated a defect classified in mechanism (2) persistent symptoms of 'faded' vision in the affected eye and long latencies in VEPs were observed, even when visual acuity had improved to 6/6 or better. We suggest that the results for our patient may follow this categorisation of responses in RBN.

Improvement in spectral sensitivity (Figs. 1A, 1B, and Table 1), Snellen visual acuity (Table 1), and achromatic flicker sensitivity at all temporal frequencies (Fig. 2) for our patient indicates that ingestion of the beer improves both luminance and colour/acuity channel response (though his highest sensitivities are still subnormal). The improvements measured indicate an increase in sensitivity of greater than 1 log unit. Frisén¹⁶ has attempted to quantify loss of visual acuity in terms of the proportional response of visual channels. In accordance with his suggestion, the variation in Snellen acuity from 6/60 to 6/9 reflects a variation in number of functional foveo-cortical channels from 0.59% to 25.3%.

Contrast sensitivity for pattern detection increased with drinking beer while the movement sensitivity remained constant (Fig. 4). This inconsistency between the two tests led to a change in the pattern to movement (P:M) ratio from 1.4 to 1.76. The P:M ratio is reported to remain normal (1.6) even in conditions such as amblyopia¹⁷ and optic atrophy,¹⁸ though MacCana *et al.*¹⁹ have described an abnormal P:M ratio of 1.23 in a case of MS. Contrast sensitivity, amplitude of VEP, flicker modulation sensitivity, and spectral sensitivity all seem to improve with drink. This may correlate with the relatively transient effects seen in mechanism (1). Movement sensitivity and latency in VEP remain constant for this patient regardless of the other improvements with drink and may be part of a second disease site referred to here as mechanism (2).

A site for the effect in mechanism (1) may be postulated from the spectral sensitivity results. In normal spectral sensitivities, increasing the brightness of the background raises the threshold across all wavelengths. The spectral sensitivity results for our patient (Figs. 1A and 1B) show no loss for any specific wavelength. The colour opponent mechanisms measured seem to be attenuated as if we had increased the background brightness 10-fold (after-

drink measurement) to 1000-fold (before-drink measurement). The observation that he uses central fixation and that the dark adaptation curve in his case shows little or no rod function excludes, we consider, the possibility of rod contribution to his spectral sensitivity responses. We might postulate that the site for improvement may be located at the area for retinal brightness control in normal photopic vision.

The VEP recorded in optic neuritis often shows prolonged latency of the major P100 wave, persisting sometimes long after recovery of visual acuity.^{20,21} The VEP results with our patient showed a significant increase in latency relative to normal even when his vision was excellent and Snellen VA was >6/9. The perceptual consequences of 'timing errors' from lesions that affect the transmission characteristics of the visual pathway—that is, VEP latency increase—may be paradoxical. Bodis-Wollner *et al.*²² found that although VEPs revealed interocular latency differences, the 'slower' eye (in terms of latency) appeared, in that specific case, to have the more sensitive response as measured psychophysically. A spatial frequency 'notch' (Fig. 4) has been described by other workers. Regan *et al.*²³ demonstrated both orientation and spatial frequency specific changes in MS. Neurones responding to particular spatial frequencies have been demonstrated only in the striate cortex. A recent nuclear magnetic resonance (NMR) study has shown that 19 out of 31 patients presenting with their first attack of isolated optic neuritis had multiple lesions, some in the occipital white matter (W. Ian McDonald, personal communication). This may account for a 'scrambling' of information at the input level of the visual cortex. Retrograde degeneration of axons damaged by RBN affords an alternative explanation. R. Hess (personal communication) has suggested that such 'dips' are due to a loss of paracentral retinal ganglion cells. Regardless of the site of damage, in the case of our patient, rapid changes in vision including loss of the dip in contrast sensitivity, indicate that the effect is reversible or that damage is not permanent.

A biochemical model for transitory changes in nerve conduction has been offered by Davis *et al.*²⁴ in relation to levels of calcium ions in patients with MS. The concept of a 'safety factor' for nerve conduction was defined as being proportional to the action potential and inversely proportional to the threshold intensity (minimal stimulus required to produce a impulse).²⁵ A lowering of the threshold intensity was achieved by decreasing ionised calcium, with a resultant improvement in visual function for MS patients. For our patient neither serum calcium nor acid-base state showed any significant changes.

It is emphasised that significant improvement of our patient's visual function was observed (Table 1

and Figs. 1A and 1B) after two control trials with beer heated to body temperature. We believe these results rule out a pure temperature (cooling) effect on nerve conduction by the beer.

A transient improvement of visual function has been reported recently²⁸: 4-aminopyridine reduced the depth of scotomata in two patients with MS. How the slight visual improvement of these MS patients relates to the dramatic improvement in our case of recurrent RBN is unknown.

CONCLUDING COMMENTS

The results of the psychophysical and electrophysiological evaluations support our patient's observations that his vision improves substantially after drinking beer. He has also observed that the 'darker' the beer the more marked the visual improvement. After more than six experimental sessions the reliability of his observations encouraged some 'home experiments' to be attempted. Using a portable Snellen chart at home, he found drinking an equal volume of orange juice or water did not increase the visual acuity. Without drinking beer, the diurnal variation in VA throughout the day (measured hourly from 10 am to 9 pm) was negligible.

Identification of the precise factor initiating visual improvement after drinking beer is problematical. Neither a trial with the alcohol equivalent to the 2.25 pints (1.3 l) of beer (by five short measures of spirit (whisky)) nor one with alcohol-free lager improved his VA. The latter observation suggests that a light distillate product responsible for this effect is removed during dealcoholisation of alcohol-free lager.

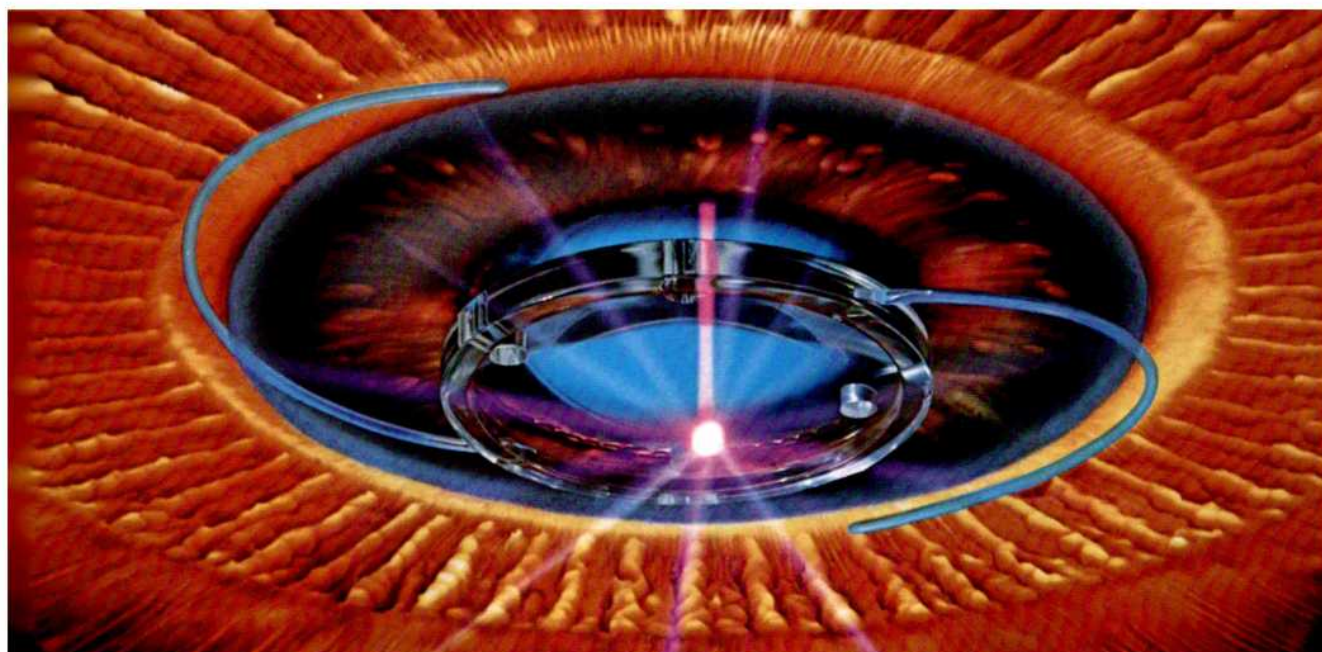
The results shown here indicate several visual parameters that were labile in our patient's condition. Further study of these factors may lead to a pharmacological means of temporary relief in the symptoms associated with recurrent retrobulbar neuritis.

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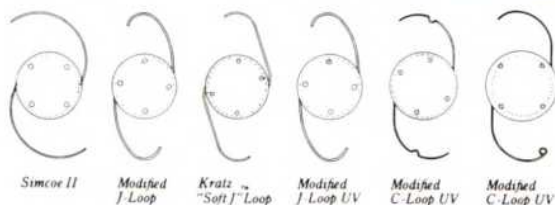


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is to be avoided.



FML: PRESCRIBING INFORMATION

Presentation White, microfine, sterile ophthalmic suspension containing fluorometholone (0.1%). **Uses** Topical ophthalmic suspension for steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **Dosage and Administration** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely. **Contra-indications, Warnings, etc.** CONTRA-INDICATIONS: Acute superficial herpes simplex keratitis. Fungal diseases of ocular structures. Vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity to the constituents of this medication. **Warnings** Steroid medication in the treatment of herpes simplex keratitis involving the stroma requires great caution. Frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with use of topical steroids. Safety and effectiveness have not been demonstrated in children of the age group two years or below. This preparation contains benzalkonium chloride and should be used with caution in association with hydrophilic contact lenses. **Use in Pregnancy** Safety of the use of topical steroids during pregnancy has not been established. **Precautions** As fungal infections of the cornea are particularly prone to develop coincidentally with long term steroid applications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intra-ocular pressure should be checked frequently. **Adverse Reactions** Glaucoma with optic nerve damage, visual acuity or field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of the globe. Local side effects of steroid therapy, i.e. skin atrophy, striae and telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Protect from freezing. **Legal Category** POM. **Package Quantities** Supplied in plastic dropper bottles of 5ml and 10ml. Basic NHS cost (as at July 1984) 5ml: £1.78, 10ml: £2.85. PL 0426-0026. Full prescribing information is available on request.

FML-NEO: PRESCRIBING INFORMATION

Presentation Sterile, white, microfine ophthalmic suspension containing fluorometholone, 0.1% and neomycin sulphate, 800.5% (equivalent to 0.35% neomycin base). **Uses** FML-NEO is indicated for the management of steroid responsive inflammation of the palpebral or bulbar conjunctiva, cornea and anterior segment of the globe, when threatened or complicated by infection with neomycin-sensitive organisms. **Dosage and Administration** One or two drops in the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosage may be safely increased to one drop every hour. Care should be taken not to discontinue therapy prematurely. Shake well before using. **Contra-indications, Warnings, etc.** Acute untreated purulent ocular infection. Acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the conjunctiva and cornea. Tuberculosis, fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As for FML above and, in addition, in diseases due to micro-organisms resistant to neomycin. Infection may be masked, enhanced or act as the steroid. Prolonged use may result in overgrowth of nonsusceptible organisms. Articles in current medical literature indicate an increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind. If an allergic or other untoward reaction occurs, discontinue the medication. **Precautions** Patients with histories of herpes simplex keratitis should be treated with caution. Use of topical steroids may increase intraocular pressure. Safety of intensive or protracted topical steroid therapy during pregnancy has not been substantiated. Local side effects of steroid therapy, i.e. skin atrophy, striae and telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Shake well before using. Do not freeze. **Category** POM. **Package Quantities** Available in 5ml plastic dropper bottles. Basic NHS cost (as at July 1984) £1.90. PL 0426-0026. Prescribing information is available on request.

*Trade Mark

A penetrating orbitocranial stab wound

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SUMMARY An unusual case of intracranial penetration of a bread knife through the orbit is described. Despite the proximity of the blade to the internal carotids, the optic nerves and chiasm, and the pituitary the patient survived with only a minimal field defect affecting the eye opposite to the entry site; otherwise no neurological or endocrine deficit was evident.

Penetrating intracranial orbital stab wounds have attracted much attention mainly because of the morbidity and mortality associated with them.¹⁻⁵ Damage to the orbital contents may result in a rupture of the globe; retinal detachment, immediate or delayed; extraocular muscle injury; optic nerve avulsion; and lacrimal gland damage. Penetration into the cranial cavity is commonly via the superior orbital fissure or optic canal, which provide direct access with no bone fracture, or through the orbital roof, which has thin bone and therefore offers little resistance. Complications of orbitocranial penetration are serious and include laceration of brain cortex by bony spicules or the penetrating object; meningitis or abscess formation; carotid cavernous fistula and false aneurysm formation; hydrocephalus; and intracranial haemorrhage. But little has been published on minor or trivial defects.⁶ The following case illustrates an interesting example of a deep penetrating stab wound causing only a minimal field defect, and that on the contralateral side to the injury.

Case report

A 28-year-old woman was admitted to the Accident and Emergency Department, having been stabbed with a 10 inch (25 cm) bread knife. On admission the knife was firmly embedded along the right infra-orbital margin to a depth of approximately 5 inches (13 cm) (Fig. 1). Attempts by friends to remove it had resulted in the handle breaking off. She was alert and orientated with no evidence of focal neurological signs. Blood and clear fluid oozed from the wound. She had difficulty in elevating the right eye. Assess-

ment of visual acuity was difficult owing to lack of cooperation, but perception of light was present and the pupillary reactions were normal. The globe was not penetrated.

Radiological examination revealed that the knife passed along the infraorbital floor, through the ethmoid sinuses and tuberculum sellae, and the tip lay in the suprasellar cistern (Figs. 2 and 3). She was transferred to the local neurosurgical unit. Penicillin and sulphadimidine therapy was begun. Bilateral carotid angiography revealed that the blunt edge was in close proximity to the right internal carotid artery and the serrated edge lying close to the left internal carotid. A right frontal craniotomy was performed, and direct inspection at frontal craniotomy confirmed these findings. After proximal and distal vascular control the knife was removed with much difficulty, and fortunately caused no visible damage to the carotid arteries, optic chiasm, or pituitary. Post-



Fig. 1 Blade in situ on presentation.

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Fig. 2 Anteroposterior skull radiograph.

operatively and at follow-up there was no evidence of neurological or endocrine deficit. Ophthalmological follow-up showed visual acuities of 6/6 in each eye with no refractive error. External signs of injury were limited to a small wound below the right eye, which healed into a virtually invisible scar. Pupillary reactions were normal. Extraocular eye movements were full. Fundal examination revealed bitemporal disc pallor. Visual field testing was carried out and indicated a small absolute inferonasal defect in the left eye, which persisted 18 months after the injury (Fig. 4). The right visual field was normal from first examination.

Discussion

Penetrating intracranial injuries characteristically cause considerable morbidity and mortality by direct damage to vital structures, circulatory compromise, or infection. Circulatory compromise may be due to direct vascular trauma, distortion of the vessel due to local effects such as haematoma formation or oedema, or vasospasm.⁵ The pathogenesis of this vasospasm is not understood.⁷ A recent report⁴ provides an excellent example of this: at open removal of an intracranial foreign body the internal carotid artery was seen to be completely thrombosed, with no evidence of external damage or direct contact with the foreign object.

The striking feature of this case is how little damage was done by the penetration of 5 inches (13 cm) of knife into an area rich in important structures—the internal carotids, the optic nerves and chiasm, and the pituitary gland. The skilled



Fig. 3 Lateral skull radiograph.

removal of the knife by the neurosurgical team after careful dissection and identification of structures resulted in no significant damage. Detailed examination showed the only deficit to be an inferonasal field defect in the left eye (Fig. 4). This is in agreement with reflex vasospasm causing reduced flow in the smaller branches of the internal carotid, which led to reversible damage to the intracranial part of the optic nerve apart from an area of permanent damage in the superotemporal portion.

The detailed blood supply to the intracranial optic nerve is still controversial. The controversy mainly surrounds the inferonasal aspect of the nerve and the relative importance of the ophthalmic artery⁸ and the

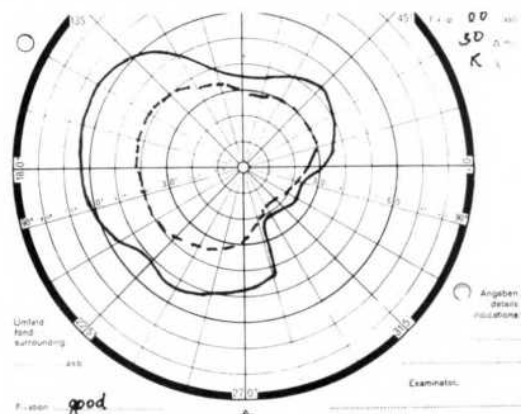


Fig. 4 Left inferonasal field defect which persists.

anterior superior hypophyseal artery.⁹ Supply to the superior and temporal parts is better agreed upon with contributions from the anterior cerebral artery, internal carotid artery, and ophthalmic artery being generally accepted.¹⁰⁻¹² The detailed account by Isayama *et al.*¹² describes the superotemporal aspect of the nerve as the only area which (a) receives only one nutrient artery, the lateral chiasmal artery, and (b) receives blood only directly from the internal carotid artery. Permanent damage to the flow in this lateral chiasmal artery either by spasm or by clot would explain the subsequent field defect in this patient. She does not notice this defect.

Damage to structures on the contralateral side to the entry wound is rarely seen. In De Villiers' series³ of 10 transorbital stab wounds only one had this complication, and the penetrating foreign body entered the lateral orbital margin and followed its anatomical direction of 45° to the sagittal plane, and thus crossed the midline.

Despite the enormous potential for serious injury the woman reported on here has survived with such a negligible defect in vision that she is unaware of its existence.

We thank Dr R McFadzean for his constructive criticism and Miss Lorna Gow for typing the manuscript.

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Luxation of the eyeball

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SUMMARY Luxation of the eyeball in two African patients is reported for its rarity. It followed minor trauma to the face and was reduced in both cases without permanent visual disability.

The following two cases of luxation of the eyeball were seen in 1983.

Case reports

CASE 1

A 27-year-old African male fell down following unexplained dizziness in the evening of 12 September 1983. He dropped on his face. When he got up he found his left eye hanging out and was unable to close the eyelids on it. In spite of dull pain he reported next morning for a medical opinion.

On examination there were no marks of injury on the forehead or face. The left eye appeared proptosed and the two eyelids hidden completely behind the eyeball. The conjunctiva was congested and chemosed. The cornea had diffused superficial haze masking a view of the interior of eye. Vision was reduced to counting fingers close to the face. The right eye was normal.

Under local anaesthesia traction was applied with the help of lid sutures applied to the lid margins. The

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eyelids were pulled over the globe and the sutures tied to achieve a sort of temporary tarsorrhaphy. The lid sutures were cut apart later the same day. The eyeball appeared less proptosed and more mobile. Tetracycline eye ointment was applied topically and the eye bandaged with a pad. Ten days later the cornea had cleared completely, and visual acuity returned to 6/9 in this eye. There was 2 mm residual proptosis and mild tenonitis at the lateral canthus at the time of discharge from hospital.

CASE 2

A 14-year-old African female hit her forehead and left eye against the glass of a window swung towards her by a sudden gust of wind on the morning of 26 September 1983. She felt some discomfort in the left eye and realised she could not close it. She reported within two hours of injury.

On examination there was no external mark of injury to her forehead or face. The left eye was proptosed, with the lid margins rolled in behind the globe (Fig. 1). Ocular movements were absent. The conjunctiva was congested and the cornea somewhat hazy. Vision was finger counting at 1 m. Only a hazy



Fig. 1 Luxation of left eyelid margins rolled behind the proptosed eye.



Fig. 2 The left eye after reduction of luxation.

view of fundus could be obtained. There was no intraocular haemorrhage.

Under local anaesthesia the lids were pulled forwards and the eyeball pressed back in place. The eye was pad-bandaged after application of tetracycline eye ointment. On the third day (Fig. 2), after reposition the proptosis was less (5 mm on exophthalmometry), and all movements except elevation had recovered. The fundus appeared normal. The central field showed a 5–7° paracentral, almost ring scotoma, some 12° from the point of fixation. She was discharged a week later with 6/6 visual acuity and full ocular movements. The central field defect continued, though reduced, till a week later. The proptosis subsided completely.

Discussion

Luxation of the eyeball is a condition in which there is forward displacement of the eye so that the eyelids close behind it. It is a rare sequel to major trauma to the orbital wall. Spontaneous luxation after trivial injury to forehead, as in our cases, is extremely rare. The factors which predispose to easy luxation include (1) shallow orbits such as are seen in infants or in cases of congenital craniofacial anomaly; (2) space-occupying lesions of the orbit; and (3) laxity of fascial ligaments and orbital muscles.¹

Both our patients were young black Africans. Lyle and McGavic² have recorded shallow orbits as a racial

factor in blacks. This could not be confirmed radiologically in our cases owing to inadequate supply of x-ray films at that time. The patients were neither obese nor the eyes prominent. There was no evidence of space-occupying orbital growth, as the eyes settled completely after reduction. Laxity of ligaments or extraocular muscles or both may also have been a contributory factor, since such anomalies have been reported in blacks by Almeida³ and Gillespie.⁴

Generally luxation does little harm if reduced early. The reduction is achieved by firmly pulling the eyelids forwards and pressing the globe backwards at the same time. Unless there is associated trauma to the bony orbit or soft tissues, timely reposition gives immediate relief and restores visual functions. The condition, though rare and seen once in the lifetime of an ophthalmologist, may perhaps be especially encountered in African patients.

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On the calculation of power from curvature of the cornea

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SUMMARY The theoretical basis for the calculation of corneal refractive power from anterior curvature is considered. It is shown that the power can be calculated with sufficient accuracy from one simple formula provided the refractive index of the 'cornea' is 1.3315. It is suggested that keratometer readings should be calibrated with this value in order to increase the accuracy in intraocular lens calculation.

In recent years the need for an exact estimation of the corneal power has arisen from the wish to control the refraction of the patient receiving an intraocular lens (IOL) implant.¹⁻⁴ Here we consider the premises of the calculation of corneal power from the anterior curvature of the cornea, as measured by the keratometer.

The principle of all current keratometers is to consider the cornea as a single refracting sphere so that the refractive power F can be calculated according to the formula for paraxial imagery:

$$F = \frac{1}{r} (n_s - n_a) \quad (1)$$

where r = radius of curvature in meters, n_a = refractive index of air ($=1.000$), and n_s = assumed value of the refractive index of the 'cornea', which in fact is the cornea and the aqueous humour combined. The value of n_s varies between various keratometers. Common values are 1.3375 (Haag-Streit, Bausch and Lomb), 1.336 (American Optical), 1.3333,⁴ and 1.332 (Zeiss). A corneal curvature of 7.7 mm will thus read 43.83, 43.64, 43.29 or 43.12 D, respectively. Since an error of 1.0 D in the corneal power will cause an error of about 1.2 D in the calculation of IOL power, it is clear that the different calibration of the keratometers might cause considerable disagreement between the IOL power calculated by different investigators.

Theory

The cornea is a two-surface system as shown in Fig. 1. The refractive power of each surface can be calcu-

lated according to formula (1), substituting for the respective refractive indices. When two surfaces of power F_1 and F_2 are combined, the following formula for the equivalent power F_{12} apply:

$$F_{12} = F_1 + F_2 - d \cdot F_1 \cdot F_2 \quad \dots (2)$$

where d equals the distance 'reduced to air' between the two surfaces. (The reduced distance d is given by $d = D/n$, where D is real distance and n is refractive index.) In this way we obtain the formula for the total refractive power of the cornea (symbols shown in Fig. 1):

$$F = \frac{1}{r_1} (n_1 - n_a) + \frac{1}{r_2} (n_2 - n_1) - d \cdot \frac{1}{r_1} (n_1 - n_a) \cdot \frac{1}{r_2} (n_2 - n_1) \quad (3)$$

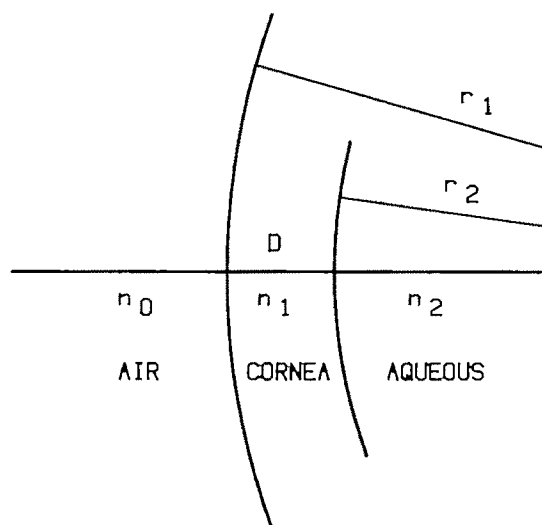


Fig. 1 The optical components of corneal refractive power.

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where n_0 =refractive index of air ($=1.000$),
 n_1 =refractive index of cornea ($=1.376$),
 n_2 =refractive index of aqueous humour ($=1.336$),
 r_1 =radius of curvature of anterior surface of cornea,
 r_2 =radius of curvature of posterior surface of cornea,
 and d =reduced thickness of cornea. When the refractive indices are known, we have three unknowns: d , r_1 , and r_2 . If necessary d , or rather D , can be obtained from a clinical measurement of the corneal thickness, that is, by pachometry. However, the curvature of the posterior surface of the cornea, r_2 , is not available from clinical methods and therefore has to be assumed.

As the first approximation we might assume the posterior curvature to relate to the anterior curvature with a constant factor k , so that

$$r_2 = k \cdot r_1 \quad (4)$$

According to Gullstrand's exact schematic eye⁴⁷ the curvature of the anterior and the posterior surface of the cornea is 7.7 and 6.8 mm, respectively. A reasonable assumption might therefore be to assume $k=6.8/7.7$.

As the second approximation we might assume a constant thickness of the cornea, which in

Gullstrand's exact schematic eye equals 0.5 mm. Inserting the constants, formula (3) now reduces to

$$F = \frac{1}{r_1} (0.3307 - \frac{1}{k} (-0.000062)) \quad (5)$$

The second part of formula (5) is a rather small value. If as the third and final approximation we assume the anterior curvature of the second part of formula (5) to be of the mean value ($=7.7$ mm), we obtain the following formula relating corneal power and anterior curvature around the mean value of the latter:

$$F = \frac{1}{r_1} (0.3307 + 0.0008)$$

or

$$F = \frac{1}{r_1} (1.3315 - 1.0000) \quad (6)$$

In other words, the most likely value of n_k in formula (1) is 1.3315.

Reliability of a simple formula

With the present day access to computers there is no a-priori reason why the calculation of corneal power should be expressed in one simple formula. The corneal power might as well be calculated in a more

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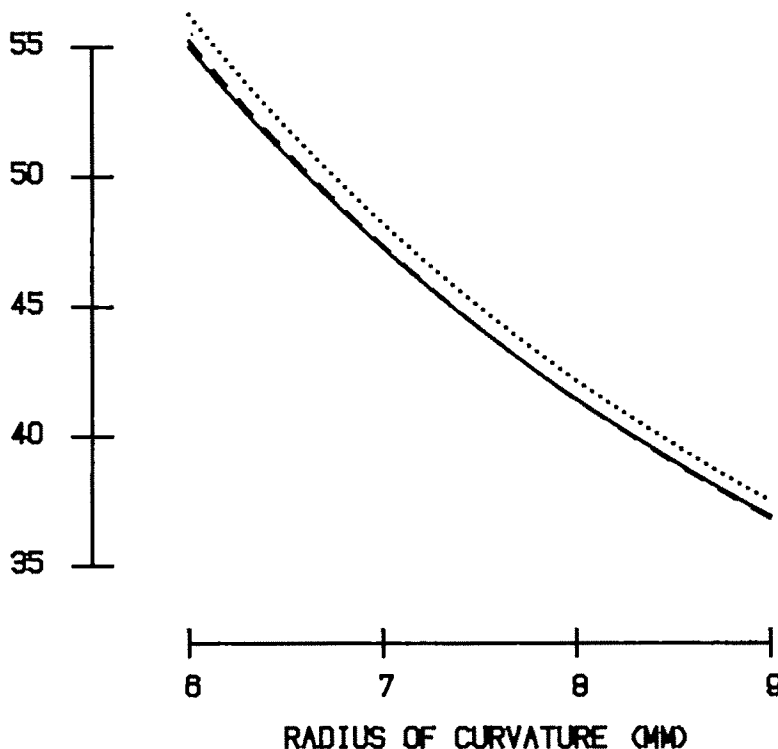


Fig. 2. Corneal power calculated from anterior curvature by means of the simple formula (1) and an assumed refractive index of 1.3315 (continuous line), as compared with the power calculated according to the more accurate formula (5) (dashed line). Included for comparison is the reading of a current keratometer which assumes a refractive index of the 'cornea' of 1.3375 (dotted line).

precise manner without unnecessary assumptions. Among the three assumptions made above, only the one regarding the posterior curvature is strictly necessary; the other assumptions are merely 'cosmetic'. Let us consider in some detail the possible errors of the assumptions made prior to formula (6).

The assumption on r_1 made from equations (5) and (6) implies that the true value of the corneal power will deviate from the value measured as the curvature deviates from the mean value. This has been illustrated in Fig. 2. Calculations show that the difference between the measured and the true value (measured value minus true value) is -0.08 , -0.04 , -0.01 , 0.00 , $+0.01$ D at $r_1=5.0$, 6.0 , 7.0 , 8.0 , and 9.0 mm respectively.

The influence of the corneal thickness on the corneal power is linear and very small. If, for example, for a standard cornea of curvature 7.7 mm and thickness 0.5 mm the thickness reduces to zero or doubles its value, the power reduces or increases by 0.1 D respectively. The error is greater for a more curved cornea.

For the standard cornea the posterior surface represents a minus lens of about -6 D. No clinical data are available on the variability of the posterior curvature of the cornea. Because the change in refractive index between the cornea and the aqueous is slight, the influence of the posterior curvature, or k

in equation (4), is also slight. It can be calculated that to increase or decrease the power of the cornea by 0.5 D the value of k should increase or decrease by 9% respectively. The error is greater for a more curved cornea.

Hence, in conclusion it can be said that the corneal power can be calculated with reasonable accuracy (within 0.1 D) from one simple formula as defined in equation (1), provided the assumed refractive index is 1.3315 . It is hoped that the use of this value may lead to greater standardisation in keratometry and in particular lead to more accurate predictions in intraocular lens power calculation.

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Indirect funduscopy in a gas filled eye: an observation

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SUMMARY It has been observed that a vitrectomised, gas filled, phakic eye can produce a real, inverted, aerial image of the fundus anterior to the cornea. The optics of this phenomenon are discussed.

Indirect funduscopy requires paraxial illumination and a condensing lens positioned at an appropriate distance in front of the eye to produce a real inverted aerial image of the fundus (Fig. 1).

The author has observed that a phakic eye filled with gas after vitrectomy can produce such an 'indirect' image without the use of a discrete condensing lens. Correspondence to Mr V T Thaller, FRCS.

In this situation the cornea/aqueous/crystalline lens complex together function as a condensing lens (Fig. 2). The image produced has all the properties of an 'indirect' image, being real and inverted, and is formed anteriorly to the cornea. It may be viewed through the operating microscope or slit-lamp microscope by focusing the instrument anteriorly from the cornea on to the image plane. The image may also be photographed by an anterior segment camera (Fig. 3).

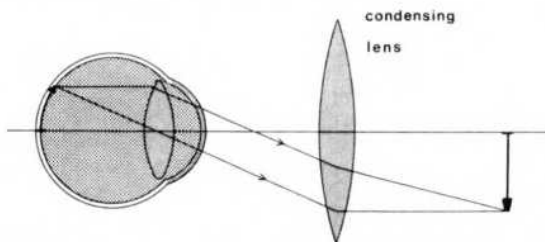


Fig. 1 Image formation by condensing lens in indirect ophthalmoscopy.

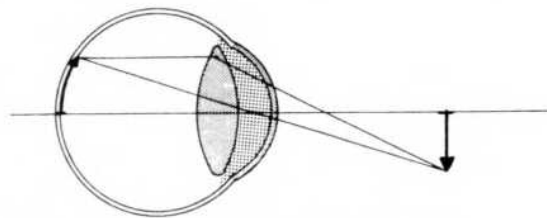


Fig. 2 Image formation by a gas filled phakic eye.

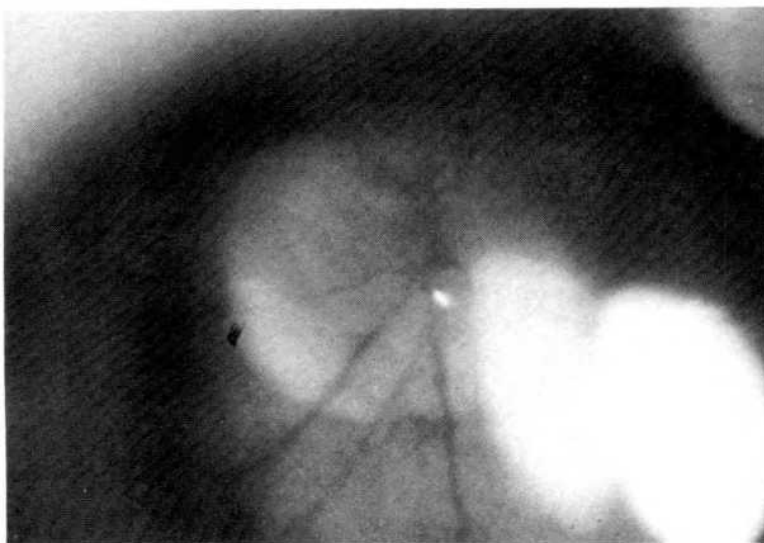


Fig. 3 Slit-lamp photograph of image formed by gas filled phakic eye. Note that plane of focus is anterior to the lids, which appear blurred. The light reflexes are the normal Purkinje images.

Optics

The total refractive power of an eye has been calculated by Helmholtz and Gullstrand¹ to be about +60 dioptres (+58.64 dioptres). When the vitreous cavity is filled with air, the posterior lens surface/air interface becomes strongly refractive. Landers *et al.*² used Gullstrand's model to calculate the refractive power of such a gas filled phakic eye and arrived at a value of approximately +100 dioptres (+102 dioptres). The cornea/aqueous/lens complex therefore acts as a +100-dioptre condensing lens forming an image I at a distance V from its nodal point N₁ (Fig. 4). The position of this image is related to the distance U between the retina (O) and nodal point N₂ by equation (1):

$$D = \frac{1}{U} + \frac{1}{V} \quad (1),$$

where D is the dioptric power of the refracting complex. From equation (1) it can be established that for the image to be formed at infinity ($\frac{1}{V} = 0$) the object distance must be 10 mm:

$$D = \frac{1}{U} \therefore U = \frac{1}{D} = \frac{1}{100} = 0.01 \text{ m.}$$

The value of U in the emmetropic eye is nearer 20 mm. In this instance the image is formed at 20 mm:

$$V = \frac{1}{(D - \frac{1}{U})} = \frac{1}{100 - 50} = 0.02 \text{ m.}$$

It follows that in myopic eyes which have a higher

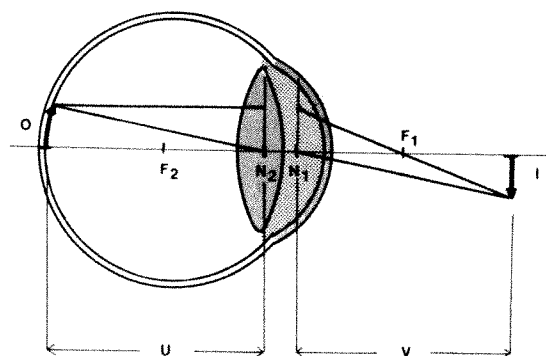


Fig. 4 The optics of fundus image projection by a gas filled phakic eye.

value of U the image will be correspondingly closer to F₁.

The clinical usefulness of this phenomenon of 'auto indirect ophthalmoscopy' of a gas filled eye remains to be established.

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Correspondence

Multiple cotton wool spots following bone marrow transplantation

SIR, B. Gloor *et al.* assert in their very interesting paper¹ that, to the best of their knowledge, 'multifocal ischaemia of retina with multiple cotton-wool spots has not yet been reported as a complication of bone marrow transplantation.'

We would like to point out to the authors that we reported in 1983² a similar case with extensive retinal and choroidal ischaemia, histopathologically confirmed, diagnosed eight months after a bone marrow graft. In this patient a thrombotic microangiopathy (Moschowitz disease) was found shortly afterwards. Then two more cases were observed (not yet published), both with retinal and choroidal ischaemia. One of them certainly had a thrombotic microangiopathy.

None of these three patients received cyclosporin A. Therefore it seems that this drug is not implicated. We think in such cases we may be in presence of ocular manifestations of thrombotic microangiopathy. This may be induced by various and combined factors: skull and/or total body irradiation, immunological disorders in relation to the graft, graft-versus-host disease, chemotherapy.

We note that choroidal involvement was found in the three cases to be associated with retinal disease. In these three cases visual impairment was the inaugural symptom, though the patients seemed to be in good health. As regards our patients the time between graft and visual symptoms is longer than in the patients of Gloor *et al.* Our three patients died shortly after eye disease developed.

In conclusion, we agree with Gloor *et al.* that 'it is clearly desirable that all patients submitted to bone marrow transplantation should be examined by an ophthalmologist'.
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SIR, We think that it is very important that Dr Binaghi informs us that in their case of extensive retinal and choroidal ischaemia, which appeared eight months after a bone marrow graft, a thrombotic microangiopathy (Moschowitz disease) has been found at necropsy and that this patient and two others, whose data are not published, did not receive cyclosporin-A. This is reassuring. What these authors found in the pathological specimen could be the possible explanation of the phenomena observed in the retina also in our cases. Nevertheless it has also to be

remembered that in no patient could any evidence of systemic thrombotic microangiopathy be found and that in all cases of our series at necropsy the vessels of the retina and the kidneys were free of obstructive disease. But this was three months to more than two years after the retinal disease had resolved.

We did not quote Dr Binaghi and co-workers' very informative paper for the following reason: we submitted the paper to the *British Journal of Ophthalmology* on 5 September 1983, before Dr Binaghi and co-workers' article appeared. We apologise that we neglected to quote the work of Binaghi and co-workers when we had to revise our paper. When it comes to priorities, we do not think that this is so important, even if we brought the first case to the attention of the haematologist with a letter to the editor in the *New England Journal of Medicine* 1983; 308: 1101 (5 May 1983) and at the Washington University Eye Alumni Meeting, St Louis, MO, on 29 April 1983. In complete agreement with Dr Binaghi and co-workers, the main goal is to watch the fundus of the eye of all patients submitted to bone marrow transplantation, to get enough information on a large sample to enable the differentiation between true disease and possible side effects of drugs, e.g., cyclosporin-A.

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B GLOOR

Ia antigen

SIR, I read with some interest the article by Roussel and Coster.¹ I doubt that the human lymphocytes that they describe were positive for Ia antigen, as these antigens are coded for by the I region of the mouse H-2 histocompatibility complex (see, for example, Hobart and McConnell²). Perhaps the authors would care to comment and correct their article.

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SIR, Although the terms Ia antigen (simply an abbreviation for immune-associated antigen) was first used to describe a system of cell-surface glycoproteins in the mouse, it has been and indeed is still widely used in the literature to refer to homologous series of antigens in other species including man.¹⁻³ The monoclonal antibody FMC 14⁴, used in this study to detect a monomorphic determinant on human Ia (probably HLA-DR) molecules, certainly does not define mouse Ia antigen. However, we take Dr Claoué's point.

The preferable modern nomenclature is class II MHC (major histocompatibility complex) antigens. It is to these antigens that we refer.

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Beauveria bassiana keratitis

SIR, I read with great interest the article on *Beauveria bassiana* keratitis by S W Sachs, J Baum, and C Mies,¹ particularly because I and my colleagues reported a case of fungal keratitis due to *Beauveria bassiana* previously.¹ I think ours was the first case of *Beauveria bassiana* keratitis, though our paper mainly reported the effects of intravenous miconazole against fungal keratitis.

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Book reviews

Child Health Care Communications. Eds. WILLIAM K FRANKENBURG AND SUSAN M THORNTON. Pp. 385. £46.00. Praeger: New York. 1984.

In the forward Dr Robert Haggerty states: 'But it is clear from several studies that many of us—even experienced clinicians have large gaps in our communication skills. We do not listen well, we are often too judgmental, we do not alter our technique to meet different needs of our patients, and we do not do enough positive reinforcement of desired

behaviors. The litany of faults in our communication skills could be very long. As a result, we do not achieve success in helping patients follow advice, and we do not integrate the skills of our disciplines for the patient's benefit.' This book attempts to emphasise aspects of communication between parents, children, and doctors, and of doctors between themselves and other people involved in the care of children. Its aims are thoroughly laudable, and despite its being the result of a colloquium it makes quite good reading. Unfortunately the price is likely to make it out of the reach of most ophthalmologists in the United Kingdom, but, if they could get hold of it, it would be a worthwhile browse for any of us involved in the care of children.

DAVID TAYLOR

Comparative Neurology of the Optic Tectum. Edited by HORACIO VANEGAS. Pp. 850. US\$125.00. Plenum: New York. 1984.

This massive volume on the optic tectum presents current information from an assortment of interesting laboratories. Initiated by workers from Brazil and Puerto Rico and catalysed by a research group at the University of Virginia School of Medicine, the book includes chapters by workers mainly in America but also Europe and Russia. The information about the tectum is immense, with chapters on development, neurophysiology, behavioural capacity, anatomy, and neuropharmacology. The book concentrates on the avian, elasmobranch, and reptilian tectum, though there are two extensive chapters on the mammalian superior colliculus.

The mammalian superior colliculus (Huerta and Harting) has been studied by all available investigative techniques. These include anterograde and retrograde transport mechanisms with either light or electron microscopic evaluation. It is interesting that the colliculus, like the geniculate, is a lamellar structure, and receives a retinal input of both Y and W cells, though the input of X cells remains controversial.

This book demonstrates again the great fascination of the visual system for research workers, and though of little practical value to the clinician it is only by keeping abreast of research today that we can improve the aspirations of our patients tomorrow.

M D SANDERS

MBL Lectures in Biology. Vol. 5. The Visual System. Eds. ALAN FEIN AND JOSEPH S LEVINE. Pp. 198. £34.00. Alan R Liss: New York. 1985.

This is a "Festschrift" in honour of Edward MacNichol, aged 65, the director of the Marine Biological Laboratory at Woods Hole, who, to judge by the preface, is expected to go on for many more happy and productive years. He himself is one of 25 contributors to a symposium which, in spite of its title, dealt almost exclusively with the retina, especially the photoreceptors. There is new information here, but also traces of déjà-vu, and, though the direct clinical relevance of some of the collected papers is circumscribed, the overall quality of the production of the book makes it highly commendable.

ROBERT WEALE

Defective Colour Vision: Fundamentals, Diagnosis and Management. By ROBERT FLETCHER AND JANET VOKE. Pp. 608. £45.00. Adam Hilger: Bristol. 1985.

This comprehensive tome is the result of a great deal of reading and quite some thought. The gamut covers such topics as how colours are seen (does anyone really know?), how colour is measured and specified, how colour vision deficiencies present, how they are acquired and, may be, passed on, etc. A great deal of attention is devoted to the description and practice of testing; this, like other sections, betrays the authors' keen interest in the history of their subject.

The practical approach to colour defects is not often treated, and therefore doubly welcome. However, Canada is not the only country where the red traffic signal is larger than amber and green, and it is a little surprising that authors, to whom the visual angle should mean a great deal, comment on this as little as on the (unquoted) fact that Switzerland has a different shape for each traffic colour.

In spite of some solecisms ('the Stiles π_4 and π_5 mechanisms, the fundamental colour mechanisms for red and green...'), the book is to be recommended. Its illustrations are helpful, its presentation good by modern standards, and the spelling of surnames largely correct. ROBERT WEALE

Laser Therapy in Glaucoma. By JACOB T WILENSKY. Pp. 148. £40.00. Appleton-Century Crofts: Norwalk, Connecticut. 1985.

The clear optical media of the eyeball have allowed examination of structures within for more than a century. With the development of lasers it was only a matter of time before the ingenuity of optical engineers and ophthalmologists miniaturised the laser light beam sufficiently to allow its use in ophthalmic work. Meyer Schwickerath, in 1956, used a xenon arc photocoagulator to produce iridectomies in aphakic eyes, while intraocular pressure control with the laser was attempted in 1972 by Lee and Pomerantz. It was not until 1981, however, that the ophthalmological community were informed of the respectability of laser treatment for glaucoma, when at the American Academy meeting corroborative reports of laser trabeculoplasty and argon laser iridectomy were presented. The nationwide interest which then developed was followed by instruction courses in laser treatment for glaucoma. This book reports on one such course that was held in March 1982 at the Illinois Eye and Ear Infirmary. It consists of the papers presented at the meeting together with some editorial comments.

The book is divided into sections, of which the largest are devoted to argon laser iridotomy and laser trabeculoplasty. Other chapters cover goniotomy, photomydriasis, and cyclotherapy. Finally there is a small chapter on the neodymium-YAG laser. All the sections are useful and instructive and contain explanations sufficiently clear to allow the inexperienced reader to perform the laser procedures described. As the book arose out of a teaching course, the writing style is relaxed and chatty and contains many references to personal technique adopted by the authors.

The book was conceived three years ago. During the gestational period the neodymium-YAG laser has proved a

more efficient instrument for making holes in the iris than the argon laser as well as having suggested roles in laser trabeculectomy and transcleral photocoagulation of the ciliary body. In addition more information on the long-term efficacy of argon laser trabeculoplasty has appeared. Despite these later developments *Laser Therapy in Glaucoma* remains a good introduction to laser treatment for glaucoma and will be of use to all ophthalmologists who wish to treat these diseases with the argon laser. ROGER A HITCHINGS

Corneal Grafting: Principles and Practice. By T A CASEY AND D J MAYER. Pp. 352. £65.00. Saunders: Philadelphia. 1984.

This book represents a major revision and expansion of its precursor, which was edited by the senior author in 1972. Although advances in corneal transplantation since that time have been rather less dramatic than those in, say, vitreous surgery, there has been significant progress in a range of aspects related to keratoplasty, such as immunology, specular microscopy, and intraocular implants, and the book provides a comprehensive review of the whole. This should ensure that its popularity is as great as before. The previous book was widely read both by ophthalmologists in training and by fully fledged ophthalmologists who dabble in corneal grafting.

After an interesting historical chapter there follow several chapters on basic sciences relevant to keratoplasty, which could well be read by anyone with an emerging interest in external eye disease. There are then chapters on eye banking and instrumentation, followed by the main part of the book concerned with indications, techniques, and complications of the various surgical procedures encompassed by 'corneal grafting,' including discussion of particular problems such as grafting in children, aphakia, and chemical burns. These are followed by chapters on refractive keratoplasty, contact lenses, and complications. Although other experts in the field would not be expected to agree with all that is written, the text is readable, misprints are minimal, and there are only a few minor irritations such as the misspelling of Terrien's and the discussion of 'rejection' with autografts. These serve more to highlight the otherwise high quality of the book. The references are plentiful and well chosen; the illustrations are profuse, and many of them are in colour. Some are poorly exposed, preventing ready identification of the point in question, but this may be a result of the need to economise on printing costs: at £65 the book represents good value. M G FALCON

Clinical Visual Optics. By ARTHUR G BENNETT AND RONALD B RABBETTS. Pp. 470. £38.00. Butterworths: Sevenoaks, Kent. 1984.

This well-produced and extended text is an update of the standard work *Visual Optics* by H H Emsley. It covers a very wide field, and its intended readership includes those in the optical profession as well as ophthalmologists.

So far as the latter are concerned, the clinical matters dealt with are variable in their completeness. It is useful for the ophthalmologist to have a reference work in which the

optical principles of many of the instruments which we use are fully and clearly elucidated. It is, however, something of a surprise to see a picture of a very old model of the Haag-Streit slit-lamp. Pseudophakia is approached in a rather academic manner, and some reference to the SRF formula and the various instruments used in computing the required power of an intraocular lens would add completeness to this section. Ultrasound is dealt with, but no indication is given of the accuracy with which one can predict the axial length of the eye. The subject of keratometry does not cover the instruments used for operative assessment, and indeed the subject of aphakic astigmatism is lightly dismissed. Some statements about clinical examination will cause a little surprise—for example, the view that it is pointless to do a cover test without spectacles if the patient wears them. At a more advanced level one might have expected to see some reference to modern surgical treatments for myopia.

It is not easy to imagine that this book will have a vital place in the library of every ophthalmologist, but it certainly should be present in major reference institutions.

J D ABRAMS

Symposium on the Laser in Ophthalmology and Glaucoma Update. Transactions of the New Orleans Academy of Ophthalmology. By H BECKMAN, D G CAMPBELL, F A L'ESPERANCE JR, M A MAINSTER, H A QUIGLEY, R N SHAFFER, R J SIMMONS, R C WATZKE, J WISE. Pp. 342. £70.00. Mosby: St Louis. 1985.

The 33rd meeting of the New Orleans Academy of Ophthalmology was held in March 1984. A symposium on glaucoma was held in 1961 and again in 1975. The latest *Transactions* covers more than just glaucoma but discusses uses of the laser in ophthalmology. There are nine participants contributing to twenty-five chapters, seventeen of which are on glaucoma with or without laser treatment. The remaining eight chapters include discussions on laser systems and photo vaporisation therapy (L'Esperance) and three chapters on laser treatment of macular disease (Watzke). However, the bulk of the topics and the round-table discussions are on glaucoma. They make no pretence to cover the subject in depth but present views of selected topics. These topics include excellent chapters on optic nerve cupping (Quigley) and pigment dispersion glaucoma (Campbell). There are also contributions reflecting the ingenuity of ophthalmologists in finding uses for the laser in the treatment of less common glaucoma conditions. The round-table discussions are good, that by Shaffer clearly a tour de force (unfortunately it is a verbatim report of a slide show and it loses much significance without illustrations).

These views are directed at the general ophthalmologist and as such prove interesting reading. Together they form a book to borrow from the library but not necessarily to buy.

ROGER A HITCHINGS

Viral Diseases of the Eye. By RICHARD W. DARRELL. Pp. 341. \$51.00. Lea and Febiger: Philadelphia. 1985.

This book contains contributions from many respected research workers in the field of ocular virology and associated infections. Most groups of viruses contain species capable of causing ocular disease. The spectrum of diseases caused include acute conjunctivitis, keratitis and blepharitis following infection of the external eye tissues, anterior and posterior uveitis following infection of the uveal tract, optic neuritis, oculomotor paresis, and meningoencephalitis following infection of the central and peripheral nervous system, and the induction of tumours. Other viruses, for example HTLV-III, while they may not directly infect the eye, may have an indirect effect by increasing susceptibility to other infections.

Individual chapters deal in turn with the various viruses responsible for ocular diseases and outline the diseases caused by these viruses, their clinical features, epidemiology, laboratory diagnosis, and methods of prevention and treatment. Eleven chapters on the herpes viruses, five on paramyxoviruses but only two on adenoviruses and single chapters on poxviruses, papovaviruses, picornaviruses, togaviruses, and orthomyxoviruses reflect the clinical concern, amount of research, and state of detailed knowledge of diseases caused by these viruses rather than their prevalence in the population. Four final chapters deal with immune mechanisms in viral ocular disease, the role of viruses in ocular tumours, the differential diagnosis of follicular conjunctivitis, and Thygeson's superficial punctate keratitis. The text is generally well supported by tables and photographs of the clinical conditions, histological sections, and electron micrographs of the viruses. There is unfortunately no index to the figures and the introduction is for some reason missing from the table of contents.

Altogether this book provides a valuable source of information on the present state of knowledge of ocular virology for both the clinician and the research worker. My only concern is that the balance of space allocated to the various groups of viruses, while inevitable, may tend to belittle the problems presented by some viruses such as the adenoviruses and picornaviruses, and concentrate research into certain popular areas like the herpes viruses. Clearly there are large gaps in our knowledge of the mechanisms of ocular pathogenicity and methods of treatment of many of the viral diseases described in this book.

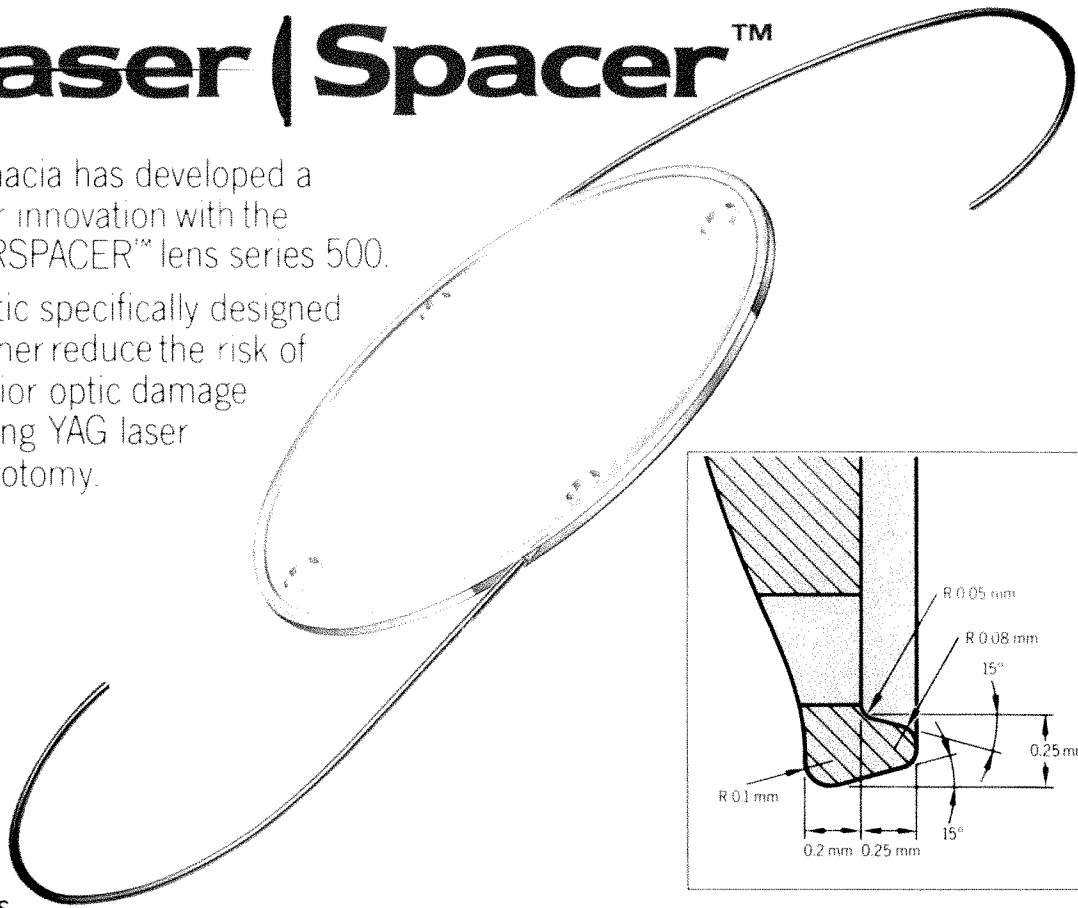
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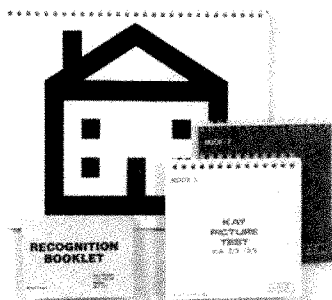
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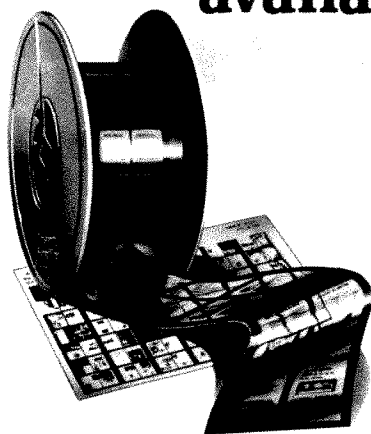
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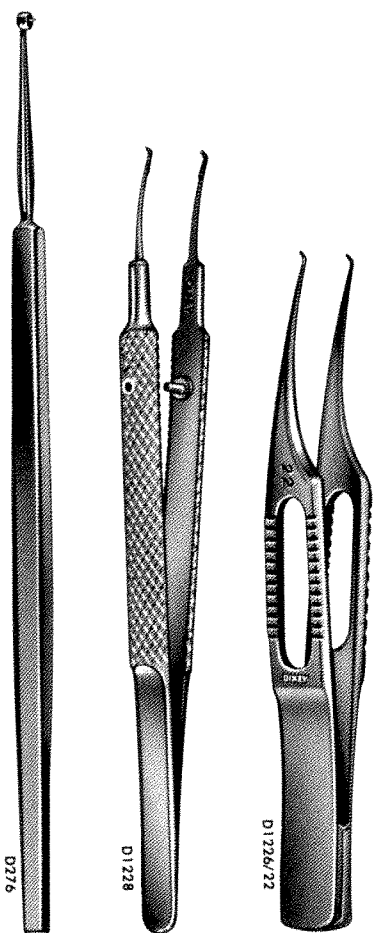
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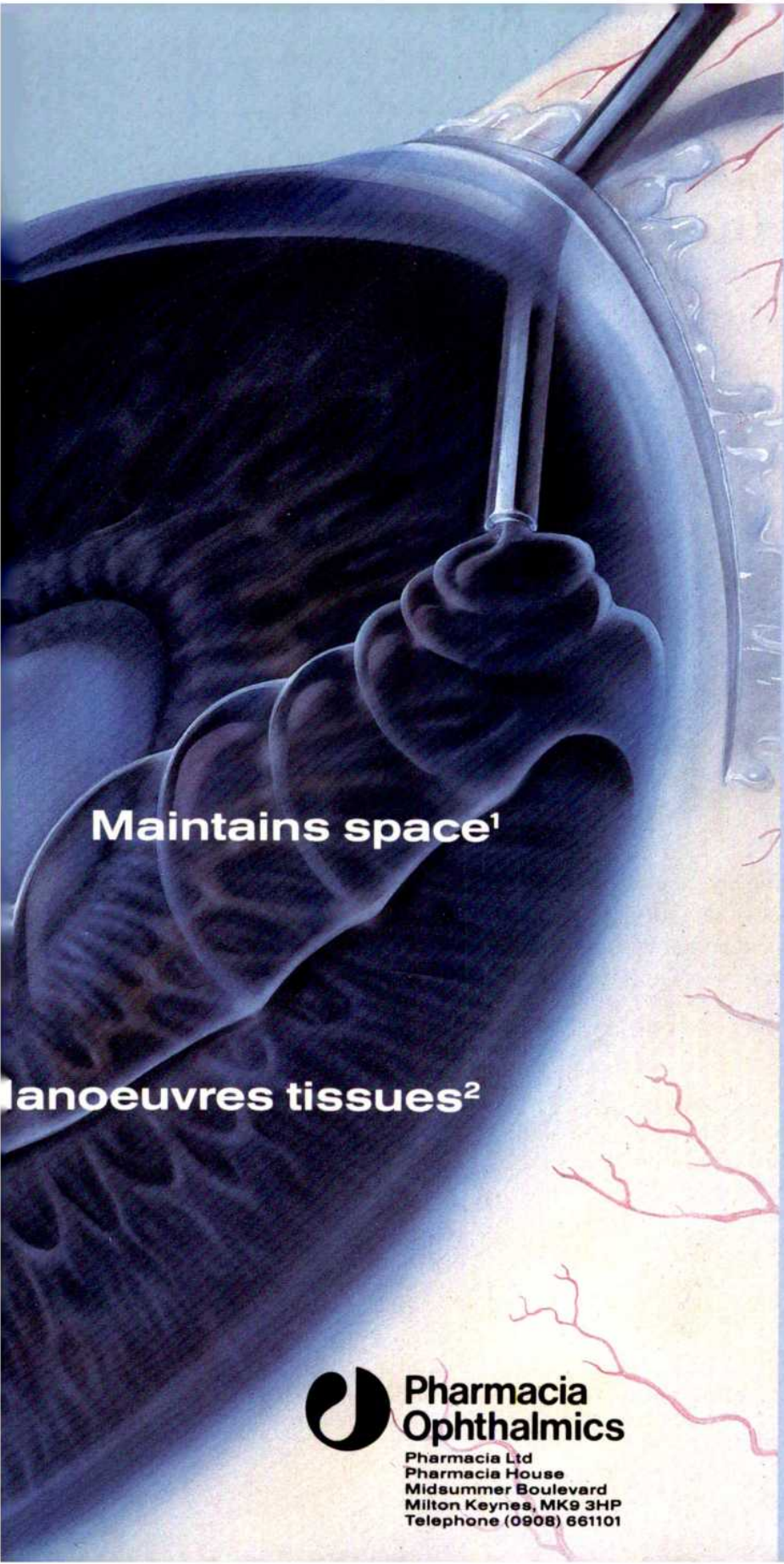
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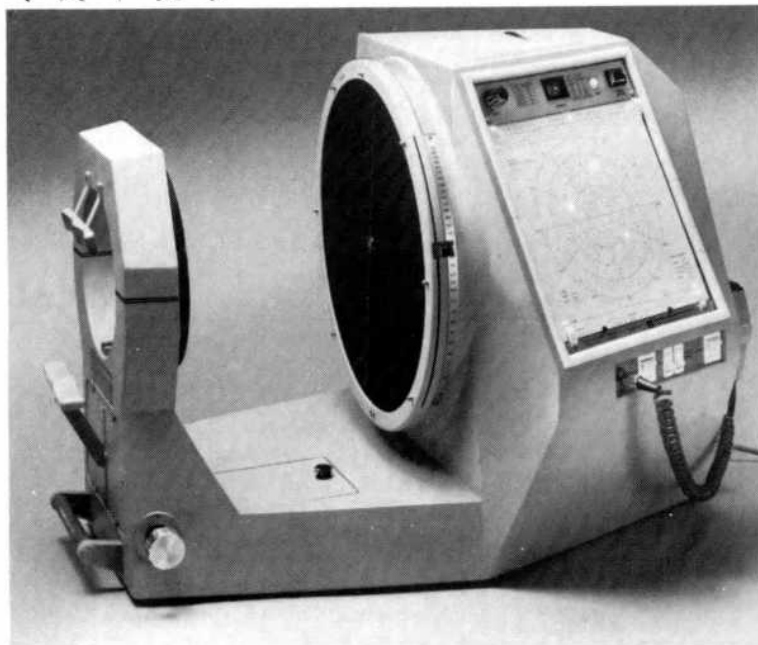
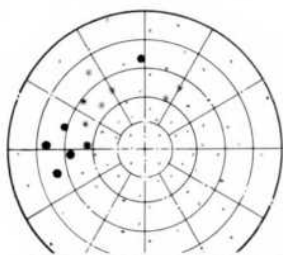
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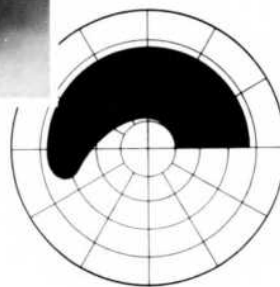
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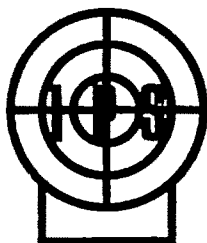
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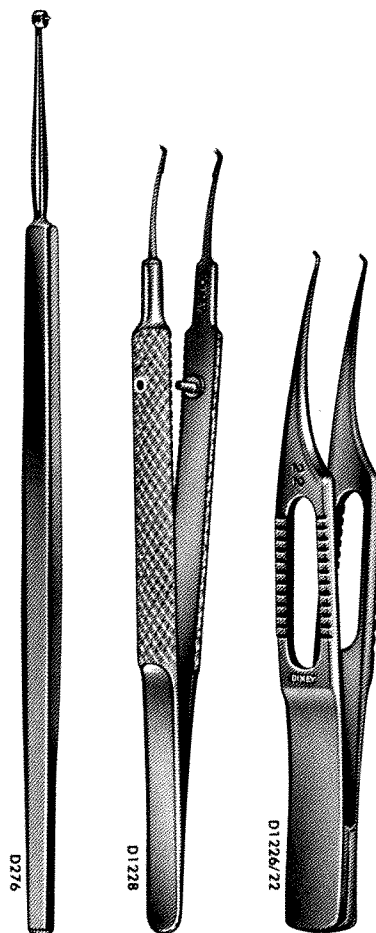
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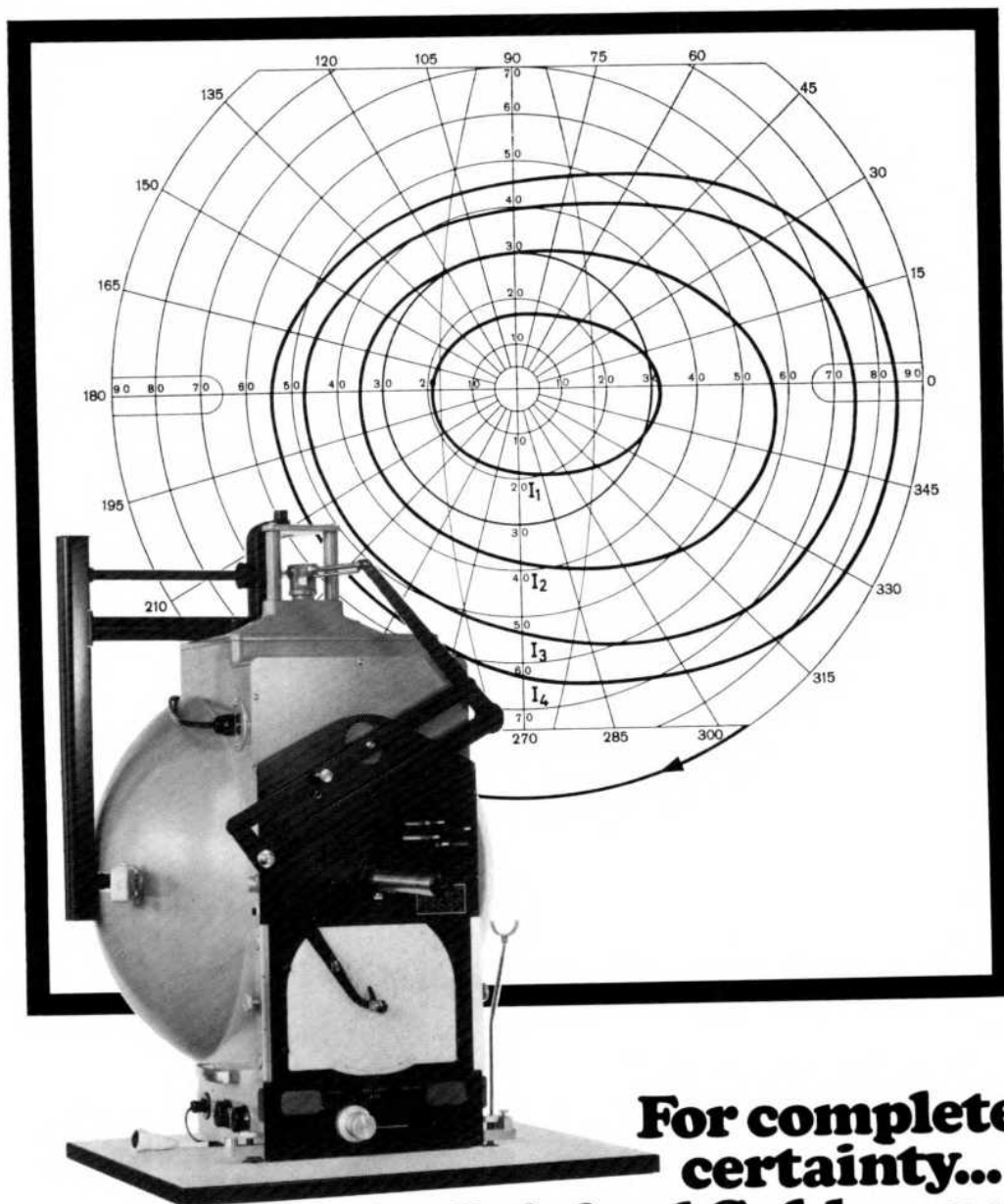
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Editorial: Neovascularisation

A simple algorithm ('rule for solving a mathematical problem in a finite number of steps'—*Chambers Twentieth Century Dictionary*) for disease might run something like this: Attack→Response→Destruction→Repair→Outcome. If you were to try to fit neovascularisation neatly into this flow-chart, you would find that it could feature in more than one section: it might be part of the response, it may certainly be part of the repair, and it may undoubtedly (in the eye), by virtue of the fragility and hence tendency of the new vessels to bleed, profoundly affect the outcome. Yet it is strange that this absolutely basic component of pathology's mechanism, which ought to rank with equal importance with the triad inflammation, neoplasm, and degeneration has hitherto not been recognised as being in the same league.

Understanding of the mechanisms of pathological neovascularisation has advanced rather slowly during the last 38 years, beginning with the observation of Michaelson in 1948 that a factor promoting vascularisation was probably present in the retina. Next in the historical sequence came retrolental fibroplasia (now retinopathy of prematurity), in which Ashton Ward and Serpell first demonstrated that the closure of retinal vasculature, paradoxically induced by the very element from which the retina was eventually to suffer lack, namely oxygen, initiated the later proliferative phase. This was followed soon afterwards, as the result of observation of the natural history of neovascularisation of the iris following central retinal vein occlusion, by the suggestion that neovascularisation on the iris was also the consequence of retinal anoxia and was mediated by a diffusible 'metabolite which stimulates new vessel formation.'

The matter does not of course end here. Neovascularisation, by virtue of its accompanying fibrosis, causes retinal destruction in the posterior part of the eye and glaucoma in the anterior, but it also has another aspect which was not initially recognised but is now obvious. Neovascularisation in the eye leads to bleeding, and in this context we have two more major categories of ocular pathology where this fundamental mechanism is almost certainly involved—diabetic retinopathy and disciform macular degeneration.

It is difficult to be certain at what point in time it

came to be realised that preretinal and intravitreal haemorrhage, which eventually leads to retinal destruction in diabetes, was due specifically to the rupture of new-formed capillaries (as opposed to previous somewhat vague theories that bleeding came from 'congested' veins). It seems likely that it must have occurred some time in the late 1950s or early 1960s. So the sequence is retinal anoxia (or ischaemia), liberation of a diffusible substance, neovascularisation, either near the retinal lesion or at a remote site, and finally bleeding, with its consequences of fibrosis and 'repair.' This may be beneficial in a fracture or a skin wound but it spells disaster in the eye.

The various elements in the story have come to light gradually, first the initial theory in 1954, then the early evidence of benefit to rubeosis by destroying a wide area of retina by diathermy in 1961 and to diabetic retinopathy by light coagulation in 1965, though the authors of this paper were actually attempting to obliterate neovascular tissue itself.¹ The first mention of light coagulation being used for its 'indirect' effect on neovascularisation (which is the mechanism widely accepted today) appears to have been in 1964 by Meyer Schwickerath² just 10 years after the original retinal anoxia hypothesis. The next important step was the demonstration of retinal ischaemia following central vein occlusion by Laatikinen and Kohner in 1976 by means of fluorescein angiography.³

Now a further link in the chain may have been forged. In a paper in this issue Taylor, Weiss, Kissun, and Garner produce evidence to suggest that they may have identified the 'metabolite which stimulates new vessel formation' in the eye, first postulated over 30 years ago. We congratulate the authors on their achievement and await with the greatest interest further studies which may confirm their important observations.

RJHS

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Effect of oxygen tension on the quantities of procollagenase-activating angiogenic factor present in the developing kitten retina

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SUMMARY Maintenance of newborn kittens in an oxygen rich atmosphere followed by a recovery period in a normal atmosphere mimicked the effects of the human disease retrolental fibroplasia. The retinas of such kittens contained significantly raised levels of low molecular weight angiogenic material (as measured by procollagenase activation) when compared with those of a control group of kittens.

It was in 1948 that Michaelson¹ first postulated the presence of a vasoproliferative or angiogenic factor in retinal tissue undergoing active vascularisation. This concept was then elaborated to include hypoxia as the immediate cause of angiogenic factor release.²⁻⁴ Thus it was suggested that chronic reduction in blood flow, sufficient to cause metabolic disturbance short of complete necrosis, would provoke the synthesis or activation of a substance able to stimulate the development of new blood vessels. It was reasoned that the substance would be easily soluble, with a molecular size sufficiently small for it to diffuse freely through the ocular tissues.⁵ On entering the vitreous gel the angiogenic substance would accumulate in the essentially stagnant environment and exercise a chemotactic effect on vessels close to the retinal surface. This hypothesis was given indirect support in subsequent years when it was shown that obliteration of ischaemic retina by photo-coagulation had a beneficial effect on accompanying neovascularisation of the iris,^{6,7} it being postulated that the soluble angiogenic factor released by the retina in this situation drained forward into the anterior chamber. Conversely it has been found that vitrectomy and lensectomy, which serve to facilitate the access of retina-derived factors to the iris, increase the risk and severity of iris neovascularisation.^{7,8}

More direct evidence in support of this hypothesis was forthcoming when it was demonstrated that

retinal extracts, not only promote angiogenesis when introduced into the cornea⁹ and chick chorioallantoic membrane¹⁰ but contain an angiogenic fraction comparable to the endothelial cell-stimulating angiogenic factor (ESAF) present in certain experimental tumours^{11,12} and arthritic joints.¹³

However, since ESAF is a feature of normal retina¹⁰ the hypothesis of a hypoxic stimulus to neovascularisation needed modification, to the extent that a quantitative increase of a factor already present had to be envisaged rather than the emergence of a new angiogenic substance.⁹ To test this revised hypothesis demanded an assay system much more quantifiable than those provided by the in-vivo systems previously used. This became possible when it was discovered that ESAF will, among other actions, activate skin fibroblast procollagenase¹⁴. This allows a quantitative assay for angiogenic activity based on collagen lysis using a radiolabelled substrate.

The relationship between other less specific growth factors which have been detected in ocular fluids and ESAF is discussed.¹⁵

In this paper we present for the first time evidence that the activity of the low molecular mass angiogenic fraction of ischaemic retina is significantly higher than that of normally perfused retina.

Materials and methods

Newborn kittens were incubated for a period of 10 days in an atmosphere containing 70-80% oxygen.

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The kittens were then allowed to recover for a period of 11 days in a normal atmosphere before being killed, when the retina was removed. A control group of kittens were maintained in a normal atmosphere throughout a 21-day period.

The retinas were homogenised for 15 s at 4°C in 50 mM NH_4HCO_3 buffer (pH 7.9) (1 ml/retina) with a glass Potter-Elvehjem homogeniser. Homogenates were centrifuged at 10 000 g for 1 h at 4°C. The supernatant was assayed for protein¹⁶ and was then subjected to ultrafiltration on a YM5 filter membrane (5000 Mr exclusion limit) (Amicon Ltd, England) with 5 volumes of bicarbonate buffer. The ultrafiltrate from single or batched retinas was reduced in volume to 5 ml, applied to a Bio-Gel P-2 column (880×22 mm) (Biorad Laboratories, England), and eluted with a 10% (v/v) solution of chromatographically pure propan-2-ol (BDH, England). The material eluting with an apparent molecular mass of between 200 to 800 was pooled and lyophilised.

Assay for procollagenase activating material was performed according to the method of Weiss *et al.*¹⁴ Assay results were expressed as μg collagen degraded/h/mg protein in supernatant. Confirmation of the angiogenic activity of the procollagenase activating fraction was obtained by the vitelline plexus test.¹⁷

Results

Extracts of both control and oxygen treated retinas gave similar profiles when subjected to Bio-Gel P-2 gel filtration chromatography (not shown). Fraction II (200–800 Mr) from both groups of kitten retinas was found to elicit a positive response when tested on the vitelline plexus (Fig. 1). Activation of procollagenase permitted a quantitative assay of this fraction from both control and oxygen treated retinas (Table 1). It was apparent that the retinas from oxygen treated kittens contained significantly raised levels of low molecular mass procollagenase activating material.

Discussion

The vaso-obliterative potential of hyperoxia in the context of the kitten retina was first demonstrated in Ashton's laboratory² and is possibly a direct toxic effect by superoxide ions and free radicals on newly formed vascular endothelium.¹⁸ On return of the kittens to normal air the retinal tissue deprived of its vasculature might be expected to suffer hypoxia and would probably become necrotic were it not for the choroidal component of its nutrition. In this circumstance the retina undergoes revascularisation from

residual vessels at the optic disc, the new vessels proliferating not only within the retina but also on its surface. It takes about 10 days before preretinal vessels can be discerned. On the assumption that the emergence of any angiogenic fraction must precede definite vessel growth, the animals were killed at 11 days into the recovery period. The control animals were of the same age.

An important component of the angiogenic process is the destruction of the collagenous extracellular matrix, through which blood vessel growth is to

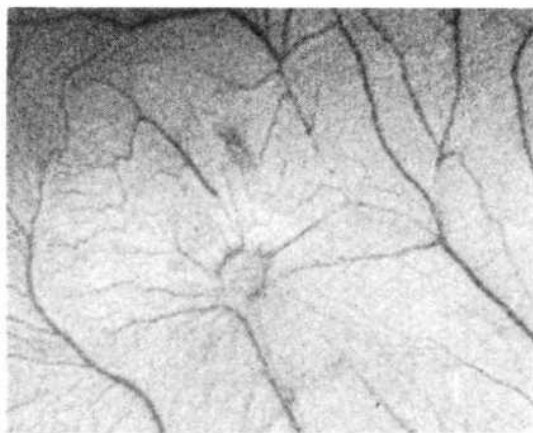


Fig. 1a

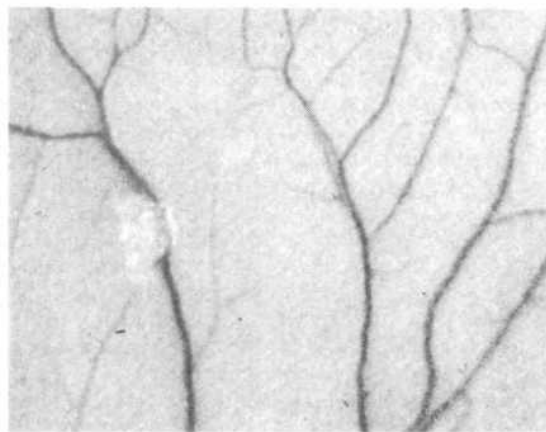


Fig. 1b

Fig. 1a Chick vitelline membranes showing the response to (a) a sample of ESAF derived from kitten retinas applied in a pellet of Elvax polymer, and (b) a control containing no ESAF in a similar pellet. Note the change in the vasculature of the test sample where vessels are drawn into the centre where the pellet has been applied. This directional realignment or reorganisation is probably the first step in angiogenesis.

Table 1 Activation of procollagenase* by retinal ESAF† derived from normal and oxygen treated kittens

Experiment	μg collagen degraded/h/mg/protein in supernatant	
	Oxygen treated	Normal, non-oxygen treated
1	2.93	0.79
2	5.24	0.31
3	3.13	0.90
4	1.11	0.56
5	2.56	0.41
6	1.03	0.64
7	0.476	0.321
8	1.49	0.80
Mean	2.24	0.59
SD	1.548	0.228
p=0.01		

Note. Experiment 1 was the sum of three pairs of retinas and experiment 2 of six pairs. All other experiments were performed on single retinas. The oxygen treated kittens were exposed to oxygen for 10 days and allowed to recover for 11 days.

*The procollagenase used in the assay had very little intrinsic collagenolytic activity; enzyme without ESAF degraded less than 0.36 μg collagen per hour.

†ESAF itself in the absence of procollagenase had no effect on the collagen substrate.

SD=standard deviation.

occur. Previous studies¹¹⁻¹⁴ have implicated the collagenolytic system in this degradative process. ESAF from all tissue so far examined has proved able to activate fibroblast procollagenase.¹² This activation has been the basis of a sensitive quantitative assay for ESAF using ³H labelled collagen as the substrate. We have been able to show a quantitative relationship between the vitelline plexus test and the procollagenase assay. The cut-off point for sensitivity on the vitelline plexus test is equivalent to an amount which would give approximately 12 μg of degraded collagen/h. Below this no activity can be demonstrated in vivo. A comparison of the procollagenase assay with activation of capillary endothelial cell proliferation shows that this test is more sensitive than the yolk sac and that activity in this system can be detected with amounts of ESAF which gave between 2 and 4 μg of degraded collagen/h.

The observation that the low molecular mass angiogenic fraction derived from both oxygen treated and control retinas had demonstrable angiogenic and procollagenase activating activity confirms previous studies on other tissues.¹¹⁻¹³

Recently¹⁵ it has been suggested that the angiogenic activity in ocular fluids is due to either epidermal or fibroblast growth factor. Although epidermal growth factor (EGF) is angiogenic in vivo and also a mitogen for capillary endothelial cells, it is a totally different entity from the low M_r ESAF described in

this paper. Firstly, EGF has a molecular mass of 6000 compared with less than 600 for ESAF. Secondly, EGF stimulation of retinal capillary cells is dependent on the cells being plated on to fibronectin coated dishes.¹⁶ Soluble fibronectin in the media did not elicit this response to EGF, and the cells also failed to respond to EGF when plated on to collagen coated dishes. This is in contrast to the effect of ESAF on retinal capillary cells, which respond and proliferate when grown on a collagen substratum in the absence of fibronectin.¹⁷ Thirdly, ESAF is not stimulatory to either fibroblast or epidermal cells. Finally, it is worth pointing out that in all cases where ESAF has been detected it has always been of similar molecular mass,¹² and there is no evidence to suggest that it is a degradation product of any other molecule.

By means of the procollagenase activation assay for ESAF ischaemic kitten retinas were shown to have more than three times the angiogenic activity of the control retinas. Whether hypoxia itself is the vital element linking reduced vascular perfusion with the stimulus to angiogenesis may be questioned. However, even if some other metabolic consequence of ischaemia, such as lactate accumulation, should prove to be involved, the contention that there is a relationship between ischaemia and angiogenesis receives considerable support from our results.

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Oral vitamin E supplements can prevent the retinopathy of abetalipoproteinaemia

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SUMMARY Six patients with abetalipoproteinaemia are described who received large doses of oral vitamin E for between 12 and 18 years in addition to a low fat diet and supplements of the other fat soluble vitamins. The progressive retinopathy observed in untreated abetalipoproteinaemia was substantially modified and most probably prevented by this therapy. Angioid streaks were noted in one patient. Treatment with vitamin A alone did not prevent or arrest the progression of the retinal lesion.

Abetalipoproteinaemia is a rare inborn error of lipoprotein metabolism.¹ The clinical features were first described by Bassen and Kornzweig in 1950² and comprise fat malabsorption, abnormally shaped red cells (acanthocytes), an ataxic neuropathy, and a retinopathy.

In 1960 three groups^{3,5} independently demonstrated the total absence of beta (low density) lipoprotein from the plasma of affected patients. Subsequently it was shown that apoprotein B, the major apoprotein of low density lipoprotein, was undetectable.⁶ As a result of the absence of apoprotein B not only low density but also very low density lipoproteins and chylomicrons cannot be formed. The lack of these three lipoproteins results in greatly reduced concentrations of blood lipids.

The defective chylomicron formation causes accumulation of triglyceride within the mucosal cells of the small intestine and results in malabsorption of fat and the fat soluble vitamins. Vitamin E is normally dependent on chylomicrons for absorption, and a major portion is transported by low density lipoprotein. In the absence of these lipoproteins vitamin E is undetectable in the serum of patients with abetalipoproteinaemia.^{7,8} There is now good evidence to indicate that the neurological features of the condition can be prevented by large oral doses of

vitamin E.^{9,11} This paper presents evidence from six patients with abetalipoproteinaemia which suggests that treatment with large oral doses of vitamin E can also prevent the development of the retinopathy.

Patients and methods

We have been following up eight patients with abetalipoproteinaemia for up to 24 years, and their treatment and progress have been reported previously.^{9,11} In all cases vitamin E was given orally in a dose of approximately 100 mg/kg/day. It varied from 47 to 172 mg/kg/day. This compares with a recommended dietary requirement of vitamin E of 8-10 mg/day.¹² The adequacy of the vitamin E therapy was regularly assessed by measuring in vitro red cell haemolysis (either autohaemolysis or peroxide haemolysis) and serum vitamin E concentrations as described previously.⁹ The haemolysis returns to normal on therapy, and serum vitamin E concentrations become detectable, though they do not reach the normal range because of the absence of low density lipoprotein.

In this study we report the detailed ophthalmological findings in six of the eight patients when they were recently re-examined. The other two patients were not available for study. The case numbers used in this report are the same as used previously.^{9,11}

Cases 1, 4, 5, 6, and 7 were examined at the Hospital for Sick Children, Great Ormond Street,

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London, and the other patient (case 8) by Dr G J B Bedford at Ninewells Hospital and Medical School, Dundee. All patients had their corrected near and distance acuity measured, their colour vision tested with the City University and Ishihara plates, and their eye position and movement examined. The external eye examination included a slit-lamp examination. Visual fields were tested by either the tangent screen or the Goldmann perimeter depending on which was more applicable.

Electroretinograms were recorded by the technique described by Calver.¹² A Medelec MS6 recording system with two-channel average was employed for the electroretinogram recording. The amplifiers had a band width of 0.16 Hz to 1.61 Hz. A Medical Devices strobe was used with the strobe head positioned 30 cm from the eyes. All recordings were made with gold foil corneal electrodes and eight or 16 responses were averaged to ensure a clean trace. The pupils were dilated with 1% cyclopentolate. The electrodes were inserted and the initial recordings made with the lights on, and then after 2, 4, 6, and 8 minutes of dark adaptation. Further recordings were made with 10, 20, and 50 Hz flicker. A normal response for this apparatus is an amplitude of more than 150 μ V from the major negative component (a wave) to the major positive component (b wave). Flicker responses should be present at all frequencies.

Results

PATIENT 1

This 14-year-old girl was diagnosed as having abetalipoproteinaemia at the age of 1 month when examined for failure to thrive. Since that time she has received supplementary vitamins A and K and large doses of oral vitamin E. One sibling (not described in this report), had abetalipoproteinaemia.

Ophthalmoscopy was normal at the time of diagnosis and on reassessment in 1975, when she was 5 years old. Between the ages of 6 and 7 years her parents noticed that her left eye was 'turning in.' She had intermittent occlusion of the right eye and had worn spectacles since the age of 4. On reassessment in 1981 she had no visual symptoms and no difficulty with night vision or with colour vision.

Visual acuity was 6/5 ($+3.50+0.50 \times 75$) in the right eye and 6/9 ($+2.50+0.25 \times 90$) in the left. Near vision was N5 in both eyes. Colour vision, tested with the Ishihara and City University plates, was normal in both eyes. A cover test showed a left alternating convergent squint of 15 dioptres for near and 10 dioptres for distance without glasses; with glasses it was 10 dioptres for near. External ocular movements were full. The pupils were equal and reacted normally to light and accommodation. Visual field exami-

Table 1 *Electroretinograms of patients with abetalipoproteinaemia after long-term treatment with vitamin E*

Case number*	Right eye amplitude	Left eye amplitude	Flicker			Result
			10Hz	20Hz	50Hz	
1	230 μ V	250 μ V	X	X	X	Normal
4	260 μ V	240 μ V	X	X	X	Normal
5	175 μ V	150 μ V	X	X	X	Normal
6	300 μ V	300 μ V	X	X	X	Normal
7	190 μ V	170 μ V	X	X	X	Normal

* Case numbers are the same as in previous reports ⁸⁻¹¹

nation by tangent screen with a 2 mm white target at 1 metre was full. Slit-lamp examination was normal. Fundus examination with the pupils dilated showed healthy optic discs, maculae, and vessels. There was, however, a very slight suggestion of increased pigmentation in mid periphery. Electrodiagnostic studies were normal (Table 1).

PATIENT 4

This 13-year-old girl was diagnosed as having abetalipoproteinaemia at the age of 11 months when she presented with failure to thrive and steatorrhoea. She has been on supplementary vitamins A and K and large oral doses of vitamin E since the time of diagnosis. Some irregularity of the pigment epithelium in both fundi was noted at the time of diagnosis, but it was thought to be normal for a fair haired baby. This appearance has remained unchanged. Visual field examination in 1979 when she was 8 years old was normal. The most recent reassessment was in 1981, at which time no visual symptoms were noted, and in particular there was no difficulty with night vision or in distinguished colours.

Examination in 1981 showed an unaided visual acuity of 6/5 in the right eye, 6/6 in the left, and a near vision of N5 in both eyes. Visual field examination showed constriction to confrontation, and generalised constriction of Goldmann perimetry to I2, I4, and II4 targets. Fundus examination showed only a diffuse pigmentary mottling in the equatorial region and a normal macular appearance (Fig. 1). Electrodiagnostic studies were normal (Table 1).

PATIENT 5

This 15-year-old girl presented at the age of 13 months with failure to thrive and steatorrhoea. She has been on supplementary vitamins A and K and large doses of oral vitamin E since the age of 16 months. Ophthalmoscopy at the time of diagnosis was normal and remained so on reassessment in 1975 at the age of 7 years. At the age of 9 years she was

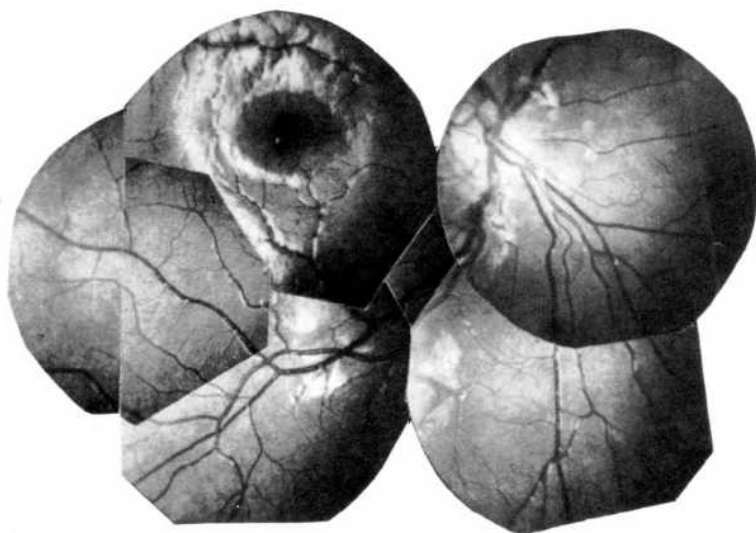


Fig. 1 Composite photographs of (A) right and (B) left fundi of patient 4. There are prominent light reflexes round the maculae and some vessels. Patients 1, 4, 5, and 6 all had fundi within normal limits.

Fig. 1A

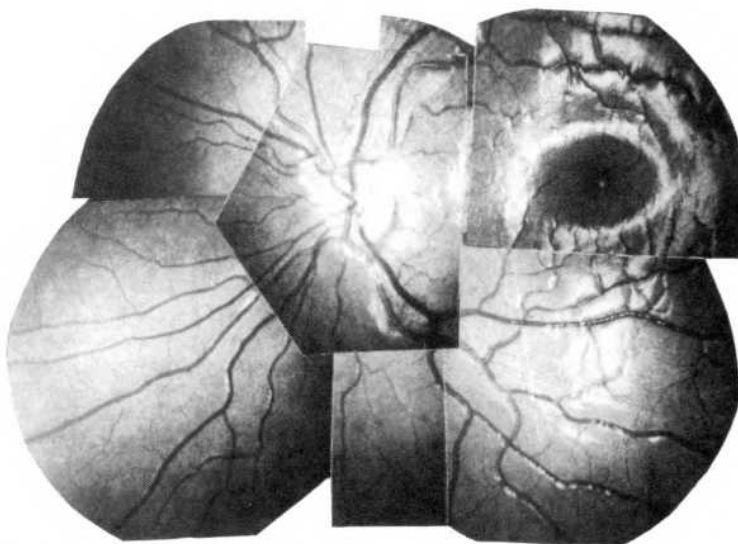


Fig. 1B

found to be myopic (there is a paternal family history of myopia) and she was prescribed spectacles. On reassessment in 1981 she had no visual symptoms apart from her myopia, which was fully correctable. She had no difficulty with night vision or in distinguishing colours.

Examination in July 1981 showed a corrected visual acuity of 6/5 (-2.0) right eye and 6/5 ($-2.00 - 0.25 \times 70$) left eye and a near vision of N5 in both eyes. Visual fields were full to a 2 mm white target at 1

metre. Fundus examination showed healthy optic discs, maculae, and vessels and no abnormal pigmentation. Electrodiagnostic studies were within the normal range as shown in Table 1.

PATIENT 6

This 20-year-old man's abetalipoproteinaemia was diagnosed at the age of 19 months after he presented with failure to thrive. He has been on supplementary vitamins A and K and large oral doses of vitamin E

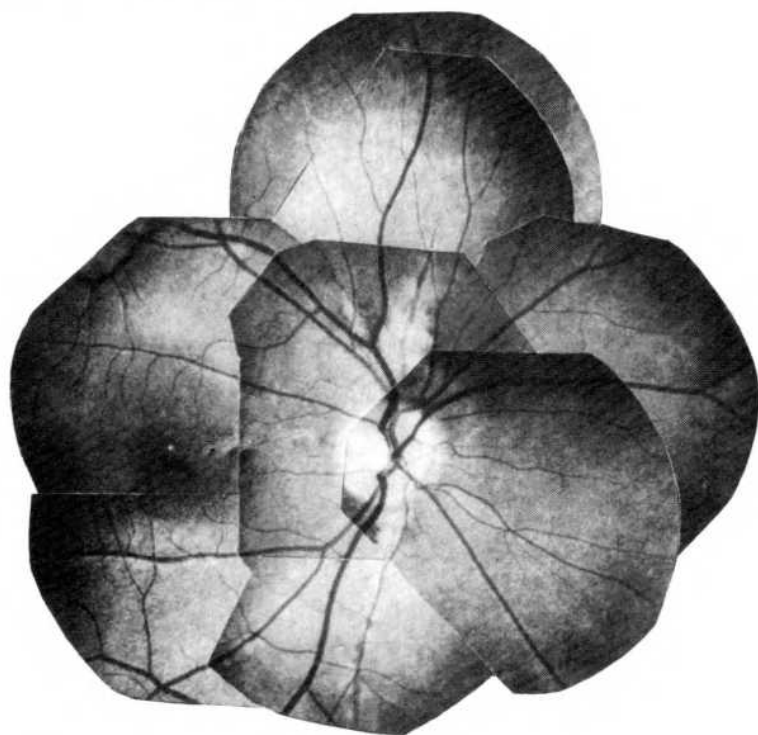


Fig. 2A

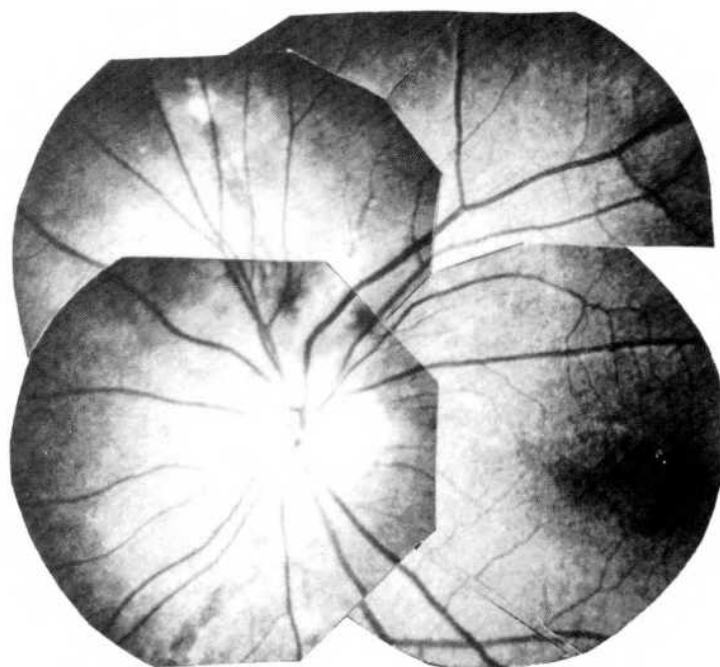


Fig. 2B

Fig. 2 Composite photographs of (A) right and (B) left fundi of patient 7.

since the age of 3 years 5 months. Ophthalmoscopy at the time of diagnosis was normal, and visual fields and electrodiagnostic tests were also normal. On reassessment in 1981 (aged 17 years) he had no visual symptoms, with no difficulty in night vision or in distinguishing colours.

On examination the unaided visual acuity was 6/5 in the right eye and 6/4 in the left. Near vision was N5 in both eyes. Visual fields, tested by a tangent screen, were full to a 2 mm white target at 1 metre. Fundus examination showed healthy optic discs, maculae, and vessels, and normal pigmentation. Electrodiagnostic studies were normal (Table 1).

PATIENT 7

This 26-year-old woman is the original patient described by Salt and colleagues in 1960³ and her condition was diagnosed at the age of 17 months, when she presented with failure to thrive and steatorrhoea. Her parents had reduced serum lipid and low density lipoprotein concentrations. She therefore probably has homozygous hypobetalipoproteinaemia, which is inherited as an autosomal dominant,¹⁰ rather than classical abetalipoproteinaemia. The two conditions appear to be clinically and biochemically indistinguishable. The only relevant family history of ocular disease was glaucoma in a parental grandfather. She received supplementary vitamins A and K from diagnosis,³ but despite normal serum vitamin A concentrations she developed at the age of 5 years a slight pigmentary retinopathy in both eyes with minimal diminution of dark adaptation. She has been receiving large oral doses of vitamin E since the age of 7 years 9 months. On reassessment in 1975, when she was 17, there had been no increase in pigmentation, and all electrodiagnostic tests of retinal function were normal. In July 1981 she complained of difficulty in adapting to subdued lighting but drove at night with no apparent problems. She had not noticed any difficulty in distinguishing colours.

On examination in 1984 the corrected visual acuity was 6/6 (−1.00) right eye and 6/6 (−1.00) left. The near vision was N5 in both eyes. Visual fields assessed by Goldmann perimetry (I2 and I4 targets) were normal. Fundus examination (Fig. 2) showed healthy optic discs, angioid streaks, and pigmentation at both maculae and in the far periphery. The vessels were normal. Fluorescein angiography (Fig. 3) confirmed the presence of angioid streaks. Electrodiagnostic studies which were normal are shown in Table 1.

PATIENT 8

This 28-year-old man's condition was diagnosed at the age of 7 years 3 months, but large oral doses of

vitamin E were not given until he was 10 years 3 months. He had been receiving vitamin E supplements prior to diagnosis, and the dosage was subsequently increased. The progression of his neurological and ophthalmological signs and symptoms while he was on vitamin A treatment alone has been noted in previous reports.^{9,14} At the time of diagnosis a pigmentary retinopathy involving the periphery was observed. Just before he began the vitamin supplements his electro-oculogram was flat. Four years later it showed a light rise of 170% in the right eye and 165% in the left, and by the age of 17 years the values were normal at 248% and 200% in the right and left eyes respectively. A bilaterally normal electroretinogram was also recorded in 1973 (at age 17 years) at Moorfields Eye Hospital. The appearance of the fundi has not changed since the time of diagnosis.

Ocular examination in 1981, when he was 25 years old, showed a corrected visual acuity of 6/9 in the right eye and 6/18 in the left. Testing of colour vision showed a mild red-green defect on Ishihara testing. The electroretinogram was within normal limits for the laboratory.

Discussion

The six patients reported on here have all been treated with large oral doses of vitamin E (approximately 100 mg/kg/day) for periods ranging from 12 to 18 years. This was in addition to their receiving a low fat diet and supplements of the other fat soluble vitamins.¹⁵ The long term results of ocular function in these patients show that the normally progressive retinal changes initially described by Bassen and Kornzweig¹ and which typically lead to blindness by early adult life have been avoided.

Over the prolonged time period of vitamin E therapy the compliance of case 1 was erratic but adequate as judged by in-vitro red cell haemolysis. In case 8 it was good until he left home, when it deteriorated and required close domiciliary supervision. The compliance in cases 4, 5, 6, and 7 was excellent.

Patients 1, 5, and 6 developed no significant ophthalmological abnormality. Patient 4 had constriction of the visual fields and mild diffuse pigmentary mottling in the equatorial region of the retina, but the ERG remained normal. Cases 7 and 8 had retinal lesions while receiving vitamin A alone, but the progression of these features was arrested after treatment with large oral doses of vitamin E.

Angioid streaks were observed in the fundi of patient 7. These streaks are breaks in Bruch's membrane,^{16,17} which are usually found either in isolation or associated with pseudoxanthoma elas-

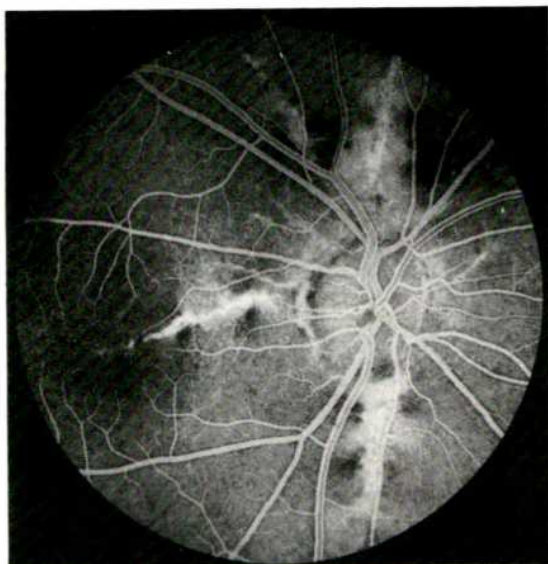


Fig. 3A

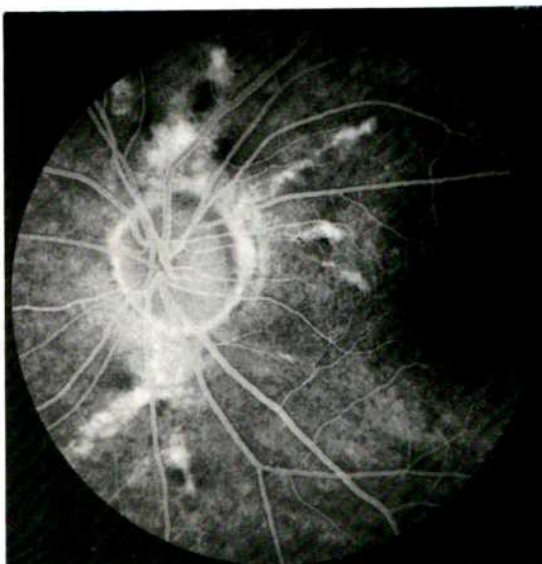


Fig. 3B

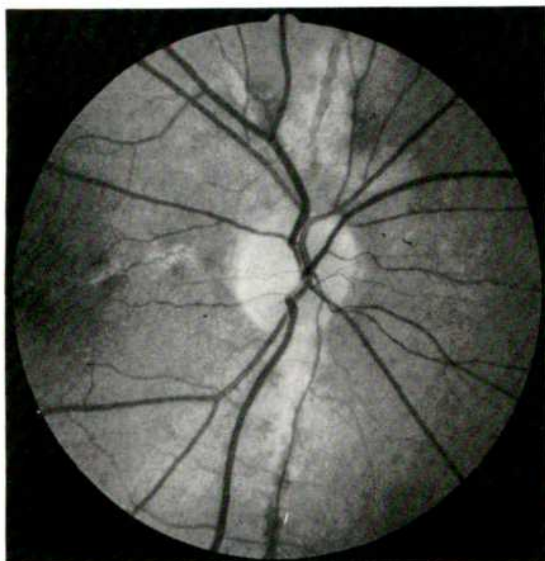


Fig. 3C

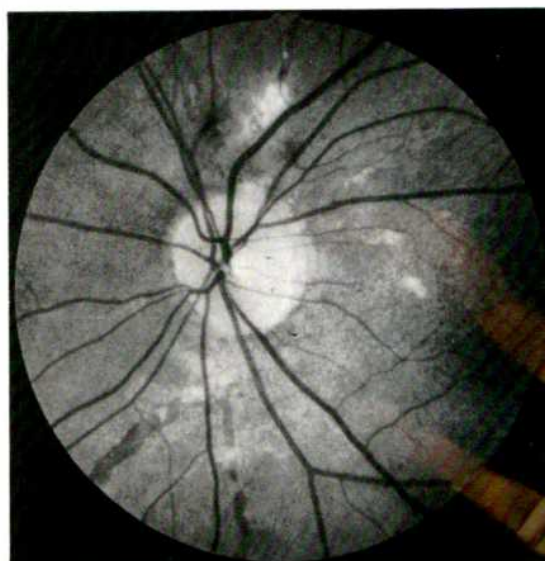


Fig. 3D

Fig. 3 Fluorescein angiograms of the fundi of patient 7. (A) Right fundus and (B) left fundus; (C) and (D) are corresponding fundal photographs.

ticum, Paget's disease of bone, sickle cell disease, betathalassaemia major,¹⁸ or hereditary spherocytosis.¹⁹ Their significance in this patient remains obscure. The occurrence of angioid streaks in several disorders with deformity of the red blood corpuscles is interesting and may reflect a common disease process, such as increased haemolysis with iron

deposition in Bruch's membrane or a defect in the structure of Bruch's membrane as a result of a common genetic defect.

There are reports of improvement in both visual signs and symptoms when patients with abetalipoproteinaemia are treated with both vitamins A and E^{20,21} and with vitamin A alone.^{22,23} The latter two

groups agreed that improvement with vitamin E occurred only in less severely affected individuals. Others, however, have reported progression of the retinal changes in patients who have been receiving sufficient vitamin A to maintain normal serum concentrations (Wolff *et al.*²⁴ reporting case 7 of the present series and Bohlmann *et al.*²⁵ Similar observations have recently been reported in a group of children with severe vitamin E deficiency secondary to chronic cholestasis who had clinical and electrophysiological evidence of retinal dysfunction despite most of them having normal serum vitamin A concentrations.²⁶ Howard and colleagues²⁷ reported on a man who had multiple resections for Crohn's disease, chronic steatorrhoea, and trace concentrations of serum vitamin E who developed ataxia and a visual field defect with pigmentary degeneration of the retina. Vitamin E therapy over a two-year period corrected both the visual field defect and ataxia. Further evidence for a role of vitamin E deficiency in the pathogenesis of the retinal lesions comes from studies on monkeys,²⁸ rats,²⁹ and dogs.³⁰ All these investigations showed that an experimental deficiency of vitamin E resulted in retinal degeneration. Robison *et al.*³¹ also examined the interrelationship between vitamins A and E and found that a combined deficiency resulted in a synergistically deleterious effect on the retina of rats.

The mode of action of vitamin E in the retina is poorly understood. Vitamin E is an antioxidant which can scavenge free radicals and thus protect membrane lipids from peroxidation. It is normally present in high concentrations in the membranes of rod outer segments of the retina,³² an area which is particularly susceptible to peroxidation. This is because it contains high concentrations of polyunsaturated fatty acids,³³ is exposed to a plentiful supply of oxygen, and light is known to enhance peroxidation.³⁴ A deficiency of vitamin E is therefore likely to accentuate peroxidative damage to the retina and also increase oxidative destruction of vitamin E.³⁵

It would appear from the long term studies in these six patients with abetalipoproteinaemia that supplementation with very large doses of vitamin E can prevent the associated retinal as well as the neurological lesions. We therefore recommend that the vitamin E status of patients with chronic and severe fat malabsorption should be investigated and vitamin E therapy instituted in order to achieve and maintain normal serum vitamin E concentrations. The vitamin E status of patients with unexplained retinal dystrophies should also be examined.

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Orbital cellulitis

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SUMMARY Forty-nine cases of orbital cellulitis were reviewed. The average age of patients at presentation was 31 years. The onset of symptoms varied from seven days or less in 28 patients, one to four weeks in 17 patients, and more than four weeks in four patients. The leucocyte count, available in 33 patients, was greater than $10 \times 10^9/l$ in only nine. Abnormal sinuses were noted radiographically in 61%. Computed tomography scans, performed on nine patients, revealed non-localised inflammation in three and an orbital mass in six. Cultures, in general, were disappointing. Seventeen surgical procedures were performed on 14 patients. The complications of orbital cellulitis, occurring in five patients, included osteomyelitis of the maxillary bone, strabismus, afferent pupillary defect, chronic draining sinus, and scarred upper eyelid. Usually the treatment of orbital cellulitis requires aggressive parenteral antibiotic therapy and judicious surgical intervention.

Orbital cellulitis is an uncommon, potentially lethal disease. Prior to the discovery of antibiotics mortality rates of 20% to 50%, and blindness in 20% to 55% of the survivors, were reported.^{1,2} Although improvement since that time has been dramatic, several series have recorded significant morbidity and mortality despite the use of antibiotics.^{3–6} A review of 49 patients with orbital cellulitis seen in the Orbital Clinic at Moorfields Eye Hospital during a 13-year period demonstrates the advantages of giving appropriate antibiotics by the intramuscular or intravenous route. There were no deaths in this series, and damage to structures within the orbit was infrequent.

Patients and methods

The clinical records of all patients with a diagnosis of orbital cellulitis between 1970 and 1983 were reviewed. Forty-nine patients (24 male, 25 female) composed the study group. Patients were included only if they had postseptal orbital inflammation considered to be caused by bacteria, if pus was drained from the orbit, or prompt resolution of the signs and symptoms followed antibiotic therapy. Patients ranged in age from 4 weeks to 71 years, mean age 31 years. Ten patients were aged 14 years or less.

All patients had radiographs of the skull, with under-tilted occipito-mental and oblique radiographs

showing details of the paranasal sinuses. In a few patients axial hypocycloidal tomograms were obtained to reveal the anatomy of the ethmoid and sphenoid sinuses. Towards the end of the review period computed tomography (CT) scans were also obtained in selected patients.

The patients were treated with a wide range of antibiotics. Those most commonly used were penicillin, synthetic penicillins effective against penicillinase-producing bacteria, ampicillin, amoxicillin, and chloramphenicol. These antibiotics were used alone or in combination, in large doses, and administered parenterally. Rifampin, ethambutol, and isoniazid were used to treat two patients who had tuberculous infections of the orbit.

Surgical drainage was performed in patients who had clinical and radiological evidence of an orbital abscess. In a number of patients sinus drainage procedures were carried out, either during the infectious period or at a later date. We included this surgery in the results only if it was performed during the period of active orbital cellulitis.

Follow-up data through complete resolution of the orbital cellulitis were available in all cases.

Results

Thirty of the 49 patients with orbital cellulitis had left orbital involvement and 17 had right orbital involvement. In two cases the orbital cellulitis was bilateral. Twenty-four of the 49 patients presented in the four

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Fig. 1 Marked eyelid oedema and proptosis in a patient with orbital cellulitis with chemosis and decreased ocular motility.

months between November and February, with fewer patients seen in the summer months.

Signs and symptoms were present for seven days or less in 28 patients, from one to four weeks in 17 patients, and more than four weeks in four patients. Two of these four patients had presumed tuberculoma of the orbit. Chemosis and eyelid swelling were present in all patients, and 45 had reduction of ocular movements (Fig. 1). The eye was displaced from its normal position in 46 patients; in the majority it was proptosed and displaced laterally or downwards. Only 16 patients had pyrexia when first seen; seven of the 16 were less than 14 years of age.

Twenty-three patients had reduced visual acuity of one Snellen line or more in the affected eye, and 20 patients had normal vision. Three patients had eyelid swelling that precluded visual assessment. In two infants vision was not assessed. One patient had an anophthalmic socket.

The leucocyte count, available on admission in 33 patients, was less than $10 \times 10^9/l$ in 24, and $10 \times 10^9/l$ or greater in nine patients (range, $5-35 \times 10^9/l$). The Westergren sedimentation rate, available in 25 cases, was 15 mm/h or less in nine patients, and greater than 15 mm/h in 16 (range 2 to 56 mm/h). Skull x-rays showed sinus abnormalities in 61% of patients, with the frontal, maxillary, or ethmoid sinuses, alone or in combination, almost equally involved (Fig. 2). Sphenoidal sinusitis was uncommon. Lytic lesions of the superior temporal orbital rim (Fig. 3) were present in two cases of presumed orbital tuberculosis. One of these lesions enlarged over an 8-month period in concert with an enlarging lung nodule. In one patient air was present in the orbit, noted at surgery to have a direct communication between the antrum and the orbit.

Computed tomography scans of the orbit were performed on nine patients. In six an abscess was shown (Fig. 4). Five of these abscesses were surgically drained, with the release of large quantities of pus, and one abscess resolved on medical therapy alone. A diffuse inflammatory reaction was shown in three patients, which later completely resolved on antibiotic therapy.

Twenty patients were on antibiotic therapy when first seen. Culture specimens were obtained from them and from most of the remainder after initiation of antibiotic therapy. Only a few cultures of blood or from conjunctiva, nose, abscess, or antrum were positive, and no one organism, or group of organ-



Fig. 2 Skull x-ray showing maxillary and ethmoidal opacification with increased orbital soft tissue density on the side of orbital cellulitis.



Fig. 3 Skull x-ray showing a superotemporal orbital rim lytic lesion in a patient with tuberculous infection of the orbit.

isms, emerged as the predominant cause of the orbital cellulitis. Cultures and stains for acid-fast bacilli in the two cases of probable tuberculosis were negative. Histological examination of the wall of one of these abscesses revealed non-specific granulomatous inflammation. Similarly, there was granulomatous inflammation with vasculitis and perivasculitis in an orbital biopsy specimen obtained from a patient



Fig. 4 Computed tomography of the orbits shows a soft tissue mass in the lateral orbit displacing the globe. Also note the contralateral eyelid oedema, which gives the impression of bilateral orbital disease.



Fig. 5 Remarkable improvement in same patient as in fig. 1, 48 hours after superotemporal transeptal orbital abscess drainage.

with positive serology and syphilitic orbital cellulitis.

Many factors may have predisposed to the development of orbital cellulitis. Eight patients gave a history of chronic sinusitis. In two patients orbital cellulitis followed sinus surgery. Proptosis suddenly developed in an 11-month-old infant, three weeks after a viral upper respiratory tract infection, rash, and uveitis were treated with steroids. Other predisposing factors included: infected chalazion (2); eyelid laceration (1); dental surgery (1); nasal septum infection (1); infected penetrating keratoplasty (1); and hypogammaglobulinaemia (1).

Seventeen surgical procedures were performed on 14 patients; the main indication for surgery was to release pus. In 12 patients the orbital abscess was incised and drained (Fig. 5); in three of these 12 patients the paranasal sinuses were drained simultaneously. Diagnostic orbital biopsies were performed in three patients. In two patients a persistent draining sinus tract was excised.

Five patients had long-term complications following orbital cellulitis: in four of them the complications were attributable to the orbital cellulitis, and in one patient, a 4-week-old infant, osteomyelitis of the maxillary bone was present after drainage of an orbital abscess. The infant was treated at another hospital and made a good recovery. In one patient sinus tract drainage from the upper eyelid persisted for eight months after incision and drainage of an abscess and for four months after the sinus tract was surgically excised. The sinus eventually closed. Vertical shortening of the upper eyelid developed after drainage of an abscess. Restricted movement of the globe developed in another patient, necessitating muscle surgery. One patient had a residual afferent pupillary defect, but retained 6/9 vision.

Discussion

Orbital cellulitis usually appears as an acute infection which, in the preantibiotic era, frequently led to blindness and even death. Sometimes these patients present with less dramatic signs and symptoms, with the result that the physician may not vigorously pursue the courses of therapy available today.^{3,4,17,18} In our series 43% of presenting symptoms were present for more than seven days, and fever was absent in 66% of patients. Similarly, laboratory data such as the leucocyte count and sedimentation rate were often normal.

It is therefore important that clinicians should be aware that orbital cellulitis may occur without signs of acute inflammation so that patients can be admitted to hospital and parenteral therapy started without delay. Chemosis, globe displacement, and decreased ocular movements are signs of orbital involvement. A complete history and a physical and ocular examination should always be performed. Predisposing factors, especially any history of sinus disease or sinus surgery, should be sought. Sinus x-rays, an integral part of the evaluation of orbital disease, should be obtained in all cases of suspected orbital cellulitis. Abnormal radiographs of the sinuses lend support to this diagnosis. The radiographic evidence of sinus disease found in 61% of our patients, with equal involvement of the maxillary, ethmoid, and frontal sinuses, is in contradistinction to the well-known predominance of ethmoid sinusitis associated with orbital cellulitis in younger children.⁷ Similarly, Schramm *et al.*⁴ noted a 74% incidence of clinical and radiographic evidence of sinusitis. This frequent association of sinusitis with orbital cellulitis may explain the higher incidence of orbital cellulitis in winter than in summer.¹⁴ Presumably the increased number of respiratory tract infections associated with the winter months would result in an increase in the incidence of sinusitis, which would then be reflected in an increased incidence of orbital cellulitis. No reason for left-sided predominance of orbital cellulitis can be determined in our series or others.¹⁴

Many patients have been started on antibiotics by the primary physician before initial referral. This was the case in 40% of our patients. Furthermore, many of the remaining patients were given antibiotic therapy after referral and prior to obtaining cultures. This probably lowered the number of positive cultures. Nasal and conjunctival cultures have not been found to help in evaluating these patients.^{3,17} Nasal cultures are rarely positive for the offending organism, though they may occasionally provide useful information in the presence of active sinus disease. Blood cultures, while seldom positive in adults (12% in Krohel *et al.*²), are more productive in the paedia-

tric population, where a 30% incidence of bacteraemia was noted by Schramm *et al.*⁴ in children under 5. *Haemophilus influenzae* was most commonly cultured in this group.

Haemophilus influenzae, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Str. pyogenes* are the commonest causes of orbital cellulitis.¹⁹ Anaerobic bacteria are not commonly searched for, but they also may cause orbital cellulitis. Fortunately these bacteria are sensitive to penicillin.¹⁴ Not surprisingly, these same organisms are listed among the commonest causes of sinusitis.¹⁹

Therapy in children under 4 years of age should include coverage of *H. influenzae*.^{17,20} Ampicillin, 200 mg/kg/day, in divided doses combined with a penicillinase-resistant antibiotic (nafcillin or oxacillin 100 mg/kg/day) should be administered parenterally. Because of the increased incidence of ampicillin-resistant strains of *H. influenzae* the use of intravenous chloramphenicol (100 mg/kg/day) should be carefully considered.²¹ In adults the initial therapy should consist of high doses of intravenous penicillin (2 000 000 units) alternating with nafcillin or oxacillin, 1.5 g every four hours. This should be given so the patient receives antibiotics every two hours. If the patient has a history of a non-anaphylactic reaction to penicillin, cefotaxime 1.2 g every six hours should be substituted. In the case of a previous anaphylactic reaction to penicillin or its derivatives clindamycin, chloramphenicol, or vancomycin may be given.²²

If the patient fails to improve on aggressive antibiotic therapy, a number of factors should be considered. The infecting organism may not be sensitive to a particular antibiotic or combination of antibiotics, and other antibiotic therapy may be started. This decision ideally would be based on positive nasal cultures in the presence of active sinus disease or on positive blood cultures; however, these data usually are not available. Computed tomography scans of the orbit should be obtained for patients unresponsive to antibiotic therapy.²⁴ If an orbital or subperiosteal abscess is present, or if the case has been misdiagnosed, and the patient has a rhabdomyosarcoma orbital pseudotumour, metastatic carcinoma with necrosis, or an atypical infective agent such as the tubercle bacillus, the CT scan will usually outline the extent of orbital involvement. Most abscesses are well localised except in acute cases evolving over 24 to 48 hours. Here CT scans may show only non-specific inflammation of the orbit, such as scleral-uvula rim thickening and muscle engorgement. When an abscess is suspected but not confirmed by CT scans, ultrasonography may confirm its presence, with its usual internal acoustic characteristics.³

Indications for surgery include unresponsiveness

to antibiotics, decreasing vision, presence of an orbital foreign body, orbital or subperiosteal abscess, and the need for diagnostic biopsy. Localisation by CT scanning best determines the surgical approach to be used. Often a combined ophthalmological-otolaryngological approach is required to establish drainage of both the sinus and the orbit. The drains are left in place until drainage stops, and intravenous antibiotics are continued for seven days thereafter.

Grave complications of orbital cellulitis, including blindness and death, still occur. Other serious complications, besides those occurring in our series, include cavernous sinus thrombosis, hypopituitarism, subdural empyema, cerebral abscess, and meningitis.^{4,5,18,25} However, aggressive, appropriate parenteral antibiotic therapy and judicious surgical intervention can considerably decrease the frequency of these serious complications.

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DESCRIBING INFORMATION

Formula White, microfine, sterile ophthalmic suspension containing fluorometholone (0.1%). **Uses** Topical ophthalmic for steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye. **Dosage and Administration** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely. **Contraindications, Warnings, etc.** CONTRA-INDICATIONS: Acute superficial herpes simplex keratitis. Fungal diseases of ocular structures. **Warnings** Steroid medication in the treatment of herpes simplex keratitis involving the cornea requires great caution. Frequent slit lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the cornea, cataract formation, posterior subcapsular cataract formation, or may aid in the establishment of ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or in the age group two years or below this preparation contains benzalkonium chloride and should be used with caution in patients with hydrophilic contact lenses. **Use in Pregnancy** Safety of the use of topical steroids during pregnancy has not been established. **Precautions** As fungal infections of the cornea are particularly prone to develop coincidentally with long term steroid use should be checked frequently. **Adverse Reactions** Glaucoma with optic nerve damage, visual acuity or field defects, subcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of cornea. Local side effects of steroid therapy in skin atrophy, striae and telangiectasia, are especially likely to affect facial skin. **Legal Category** POM. **Prescribing Information** Protect from freezing. **Legal Category** POM. **Package Quantities** Supplied in plastic dropper bottles of 5ml and 10ml. Basic NHS cost as at July 1984: 5ml £1.79, 10ml £2.93. Pl. 0426-0028. Full prescribing information is available on request.

FML-NEO: PRESCRIBING INFORMATION

Formula Sterile, white, microfine ophthalmic suspension containing fluorometholone (0.1%) and neomycin sulphate (0.35% neomycin base). **Uses** FML-NEO is indicated for the management of steroid responsive inflammation of the palpebral or bulbar conjunctiva, cornea and anterior segment of the globe, when threatened or complicated by infection with neomycin sensitive organisms. **Dosage and Administration** One or two drops in the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to one drop every hour. Care should be taken not to discontinue treatment prematurely. Shake well before using. **Contraindications, Warnings, etc.** Acute untreated purulent ocular infections. Acute superficial herpes simplex keratitis. Fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As for FML, above and in addition in diseases due to micro-organisms resistant to neomycin infection may be masked enhanced or activated by the steroid. Prolonged use may result in overgrowth of non-susceptible organisms. Articles in current medical literature indicate an increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind if sensitivity or other untoward reactions occur, discontinue the medication. **Precautions** Patients with histories of herpes simplex keratitis should be treated with caution. Use of topical steroids may increase intraocular pressure. Safety of intensive or protracted use of FML-NEO in pregnancy has not been substantiated. Local side effects of steroid therapy, ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Shake well before using. Do not freeze. **Legal Category** POM. **Package Quantities** Available in 5ml plastic dropper bottles. Basic NHS cost as at July 1984: £1.80. Pl. 0426-0045. Full prescribing information is available on request.

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FMNE 1



Adrenaline



Pilocarpine

ABRIDGED PRODUCT INFORMATION

Full prescribing information is available and should be consulted before prescribing.

USES

Elevated intra-ocular pressure including: ocular hypertension, chronic open-angle glaucoma (including aphakia); secondary glaucoma.

DOSAGE AND ADMINISTRATION

Usually one drop 0.25% solution in affected eye twice a day. If necessary change to one drop 0.5% solution twice a day.

CONTRA-INDICATIONS

Bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock. Hypersensitivity.

PRECAUTIONS

'Timoptol' may cause side effects of systemic beta-blockade. Cardiac

failure should be adequately controlled before prescribing. History of severe cardiac disease requires monitoring for cardiac failure and checking of pulse rates. Respiratory and cardiac reactions (including death) have been reported.

Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade. Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most cases clear on withdrawal. If seen, beta-blockers should be withdrawn gradually.

Do not use in patients with soft contact lenses.

Mydriasis resulting from use of 'Timoptol' with adrenaline reported occasionally. Potentially, hypotension and/or marked bradycardia may result from addition of 'Timoptol' to a calcium antagonist, rauwolfia alkaloid or beta-blocker.

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PRODUCT LICENCE NUMBERS

0.25% Ophthalmic Solution 'Timoptol': 0025/0134.

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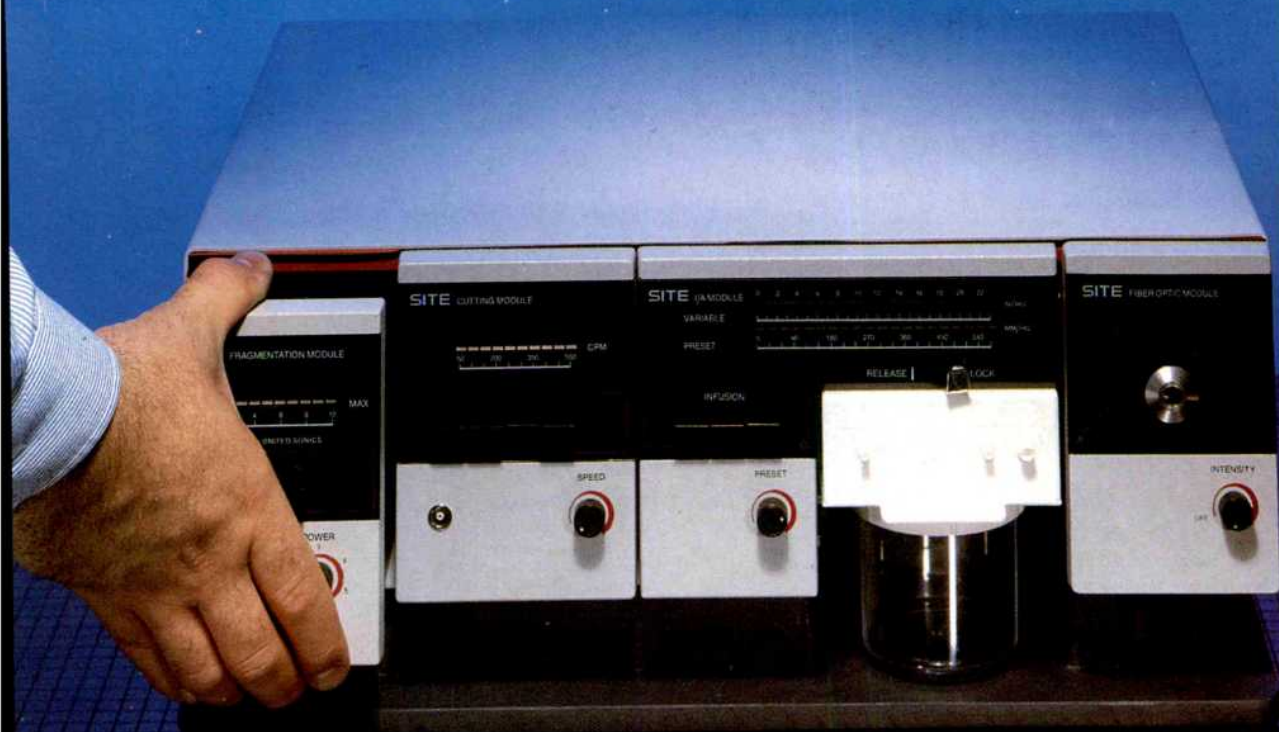
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Childhood chiasmal gliomas: update on the fate of patients in the 1969 San Francisco Study

RICHARD K IMES AND WILLIAM F HOYT

From the Neuro-ophthalmology Unit, Departments of Neurological Surgery, Neurology, and Ophthalmology, University of California, San Francisco, San Francisco, California, USA

SUMMARY We review the current status of 28 patients with chiasmal glioma who were originally reported on by Hoyt and Baghdassarian in 1969. The median period of follow-up was 20 years. Sixteen patients are now dead, five from chiasmal glioma and the rest from other causes. Four of the five deaths from chiasmal glioma occurred before 1969. The mortality rate in patients with neurofibromatosis and those without neurofibromatosis was essentially the same. Nine of 16 patients with neurofibromatosis are dead, two from chiasmal glioma, one from aspiration, and six from another tumour. Seven of 12 patients without neurofibromatosis are dead, three from chiasmal glioma, two from an operation on their tumour, and two from a medical illness. In general the quality of life of the surviving patients is good; none reported having a noticeable decrease in vision since 1969.

In the report of their series in 1969 Hoyt and Baghdassarian¹ reviewed the clinical course of 36 optic gliomas of childhood, 29 of which involved the chiasm. They stressed that, in the natural course and despite treatment of any form, these tumours appeared to have a self-limited pattern of growth and morbidity, and that the prognosis for a long survival with useful vision was good. Fifteen years have passed since that series was published. Because rational management of a childhood chiasmal glioma must be based on knowledge of its long-term behaviour, and of the generalised condition of neurofibromatosis with which it frequently is associated, we reviewed the current status of the patients in that study who had chiasmal involvement.

Material and methods

PATIENTS

Of the 29 patients with chiasmal glioma reported in 1969,¹ 28 (12 male, 16 female) are included in this study. The remaining patient is excluded now because later evaluations cast doubt on the original diagnosis.

The diagnosis of chiasmal glioma had been established histologically in 16 of the patients in this series

and was based on observations at craniotomy in four. The diagnosis was presumptive in eight patients, all of whom were children who had neurofibromatosis, loss of vision, optic canal enlargement, and optic atrophy. Five of these children had an anteriorly situated mass in the third ventricle that involved the chiasm and one or both optic nerves, as shown by tomographic pneumoencephalography; two had sphenoid dysplasia and a J-shaped sella; and one had amblyopia and a temporal field defect.

METHODS

Follow-up data were obtained by direct contact with the patients, their parents, or their physician, or from hospital records. For patients who had survived the visual function was assessed on the basis of whether the patient could see well enough to read, drive, or recognise objects. Change in visual function was estimated by asking if vision had deteriorated since 1969. Quality of life was assessed subjectively on the basis of the patient's visual capacity, degree of independence, marital status, and level of education.

Results

The period of follow-up for the present report ranged from 0 to 44 years (median 20 years). The information obtained is current to July 1984, except in the

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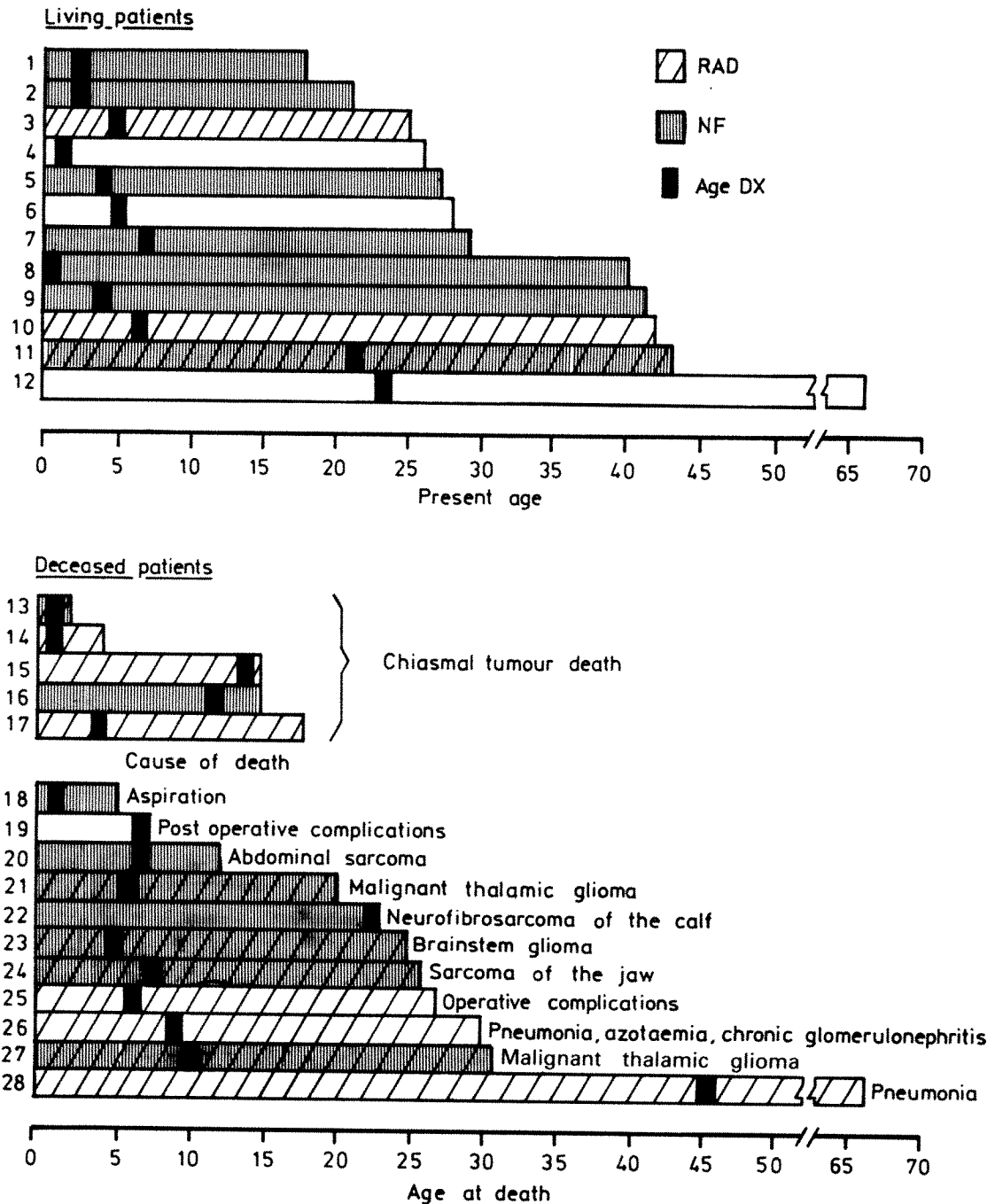


Fig. 1 Bar graph summarising data for the patients studied. Age of surviving patients is current to 1984, except for patients 1 and 7, for whom data were available only to 1975 and 1981 respectively.

case of patients 1 and 7, for whom data were available only to 1975 and 1981 respectively.

Deaths. When this series originally was reported in

1969, eight of the 28 patients were dead; eight more patients had died by the time of this review in 1984 (Fig. 1). The ages at death were distributed evenly

between 2 and 31 years, except that one patient died at the age of 67. Five patients died of their chiasmal tumour; only one of these died after 1969. Most of the deaths in the series were from other causes.

Causes of death in patients with or without neurofibromatosis. Nine of the 16 deaths occurred in patients with neurofibromatosis. Two patients died from their chiasmal tumour at 2 and 15 years of age respectively. All deaths from non-chiasmal tumours occurred in this group: three patients died from sarcomatous degeneration of peripheral neurofibromas at 12, 23, and 26 years of age, and three others from a malignant glioma of the brain at 20, 25, and 31 years of age respectively. One patient aspirated fluid and died at age 5 years after removal of lingual and cervical neurofibromas.

Seven of the 16 deaths occurred in patients who did not have neurofibromatosis. Three of them died from chiasmal tumour at 4, 15, and 18 years of age, and two as a direct result of operations on their chiasmal tumour at 7 and 27 years of age respectively. Two died of medical illnesses: one of pneumonia, azotaemia, and chronic glomerulonephritis at 30 years of age, and one of pneumonia at age 67 years.

Causes of death in patients treated with or without radiation. Eleven of the 14 patients who received radiation therapy died, four from their chiasmal tumour at 2, 4, 15, and 18 years of age respectively, and the rest from other causes. Five of the 14 patients who did not receive radiation therapy died, one of her chiasmal tumour at 15 years of age and the rest from other causes.

Surviving patients. The 12 patients surviving at the time of this review ranged from 17 to 66 years of age; most were between 25 and 45 years old (Fig. 1). They have been followed up for 14 to 44 years (median follow-up 23 years). The diagnosis of chiasmal glioma had been established histologically in six of these patients, by observation at craniotomy in two, and by tomographic pneumoencephalography in four. Seven of the patients had neurofibromatosis. Three received radiation therapy.

In general these patients had a good quality of life. Five had married and were raising families; three were college graduates, one with a master's degree. Most were self-sufficient and could see well enough to read and/or drive, and most were employed. No patients reported that their vision had deteriorated noticeably since 1969.

Discussion

This study represents the longest follow-up review of patients with chiasmal glioma yet reported. The 28 patients have been followed up for a median of 20 years since diagnosis. Sixteen of those patients

(57%) are dead. Although this mortality rate is higher than that reported for other series, only five of our patients (18%) died from their chiasmal glioma. Four of the deaths from chiasmal glioma occurred before 1969, each within three years of diagnosis; the other occurred 14 years after diagnosis. This result suggests that the risk of death from a chiasmal glioma is greatest during the early follow-up period. Such a possibility is reflected also in the findings of Rush *et al.*² Calculating the probability of survival in their 52 patients with chiasmal glioma, Rush *et al.*² showed that the greatest risk of death was in the first decade after diagnosis. The 27 deaths from chiasmal glioma in their series occurred a median of four years after diagnosis, and their 23 surviving patients were alive a median of 17 years after diagnosis.

Our data do not support the suggestion made by Stern *et al.*³ in 1979 that optic glioma in patients with neurofibromatosis occurs preferentially in the optic nerve without involvement of the chiasm. Sixteen of our patients (57%) had neurofibromatosis. Among the other reported series of patients with optic chiasmal glioma, eight of 18 patients (44%) reported by Oxenhandler and Sayers,⁴ 14 of 32 patients (44%)* reported by Lloyd,⁵ 15 of 38 patients (39%)* reported by Miller *et al.*,⁶ 10 of 26 patients (38%) reported by DeSousa *et al.*,⁷ and six of 18 patients (33%) reported by Danoff *et al.*⁸ had neurofibromatosis. Nor do our results support the notion that the presence of neurofibromatosis has a protective influence on survival, as was suggested by Rush *et al.*² The mortality rate for our patients who had neurofibromatosis (9/16, or 56%) was essentially the same as that for our patients who did not (7/12, or 58%).

It appears in fact that such patients with neurofibromatosis may be at a greater risk of death from a non-chiasmal tumour than from their chiasmal glioma. Of our nine patients with neurofibromatosis who died only two died from their chiasmal glioma, whereas six died from other tumours—most within the second or third decade of life (Fig. 1). Moreover, all the deaths from a second tumour in our series were of patients with neurofibromatosis. There are several other reports of death from other tumours in children who had the combination of neurofibromatosis and chiasmal glioma: one child died of fibrosarcoma of the temporal lobe five years after discovery of the chiasmal glioma,⁹ one of a malignant peripheral nerve tumour 13 years after chiasmal glioma was diagnosed,⁴ and one of a cerebellar astrocytoma eight years after diagnosis of the chiasmal tumour.²

While many of our patients initially had a significant degree of visual impairment, their visual function has not changed appreciably since diagnosis.

* Our calculation from data provided in the article.



Rush *et al.*² reported essentially no change in the visual acuity in the better eye of their 52 patients with chiasmal glioma from the initial to the final examination; Wong and Lubow⁹ reported that, except for patients who underwent a surgical procedure, their patients' vision remained relatively stable during the follow-up period. Glaser *et al.*,⁸ reviewing 20 of the patients from our series in 1971, noted a monotonously stable course of field defects and visual acuity in most patients; in addition they found no perimetric evidence to support the efficacy of irradiation in those patients. All of these findings corroborate Hoyt and Baghdassarian's¹ earlier suggestions that visual impairment present at the time of diagnosis does not change appreciably thereafter.

Our review shows that nine of the 12 survivors in this series had no radiation therapy, whereas 11 of 16 patients who died, including four of the five who died from their chiasmal tumour, had undergone irradiation. Our series, however, affords no conclusive answers regarding the benefits or hazards of radiation therapy for these tumours. The two deaths after neurosurgical procedures in our series occurred in the immediate postoperative period; one early in the series was from hypothalamic complications and the other late in the series was the result of a carotid artery injury. We believe that both deaths were avoidable.

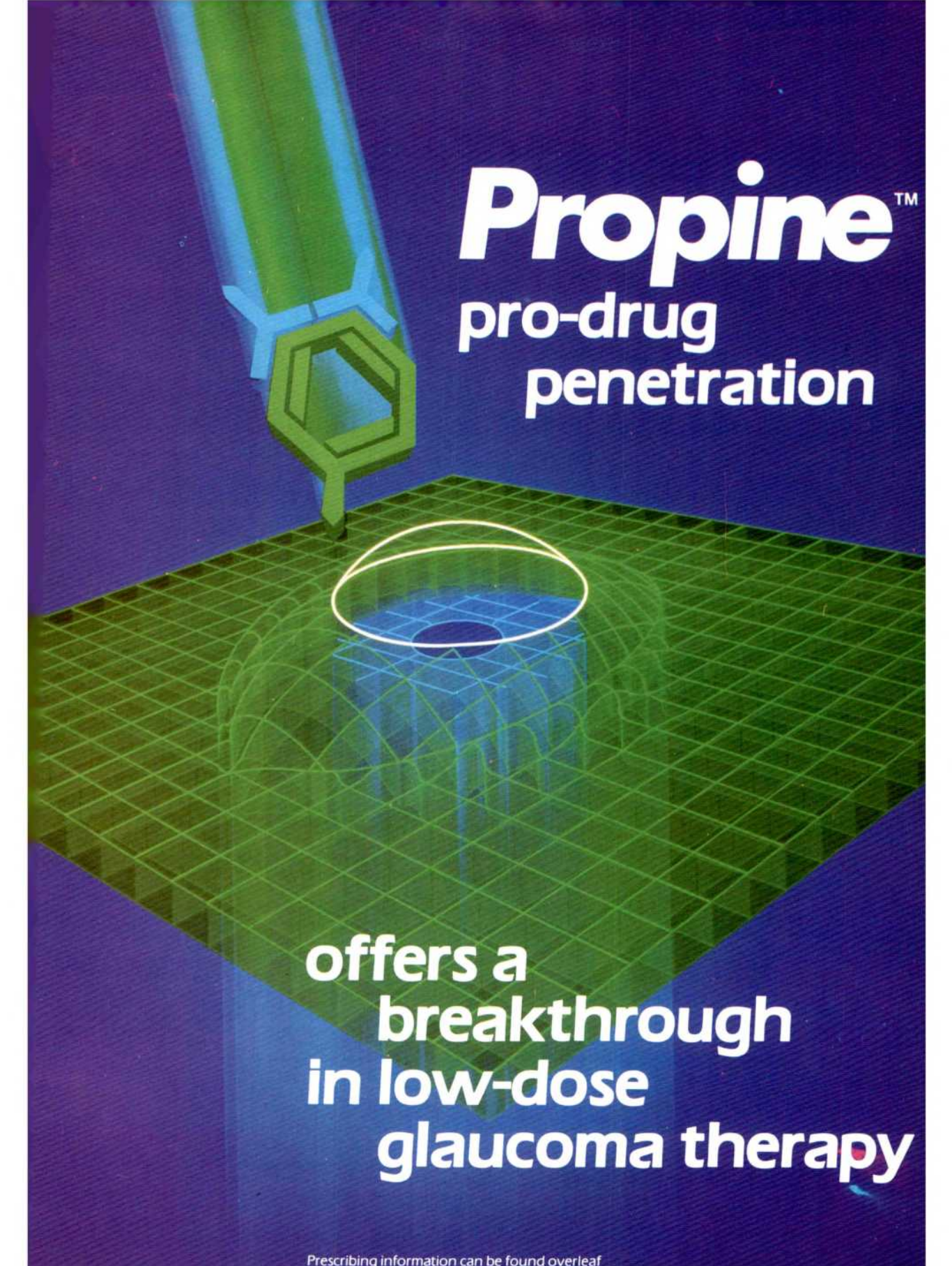
Except for the hypothalamic effects on growth and body habitus most of our surviving patients are normal, healthy, functioning members of society. We

find, however, that the prognosis for survival in patients with chiasmal glioma is not as good as it was thought to be in 1969. For such patients with neurofibromatosis the poorer prognosis is not a factor of the chiasmal glioma, but of the potential for development of a malignant tumour elsewhere in the brain or in the peripheral nerves.

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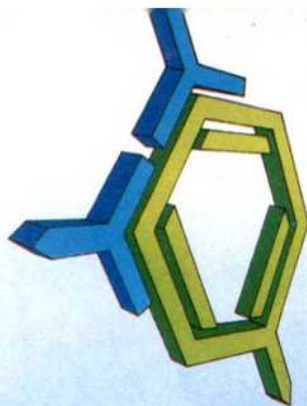


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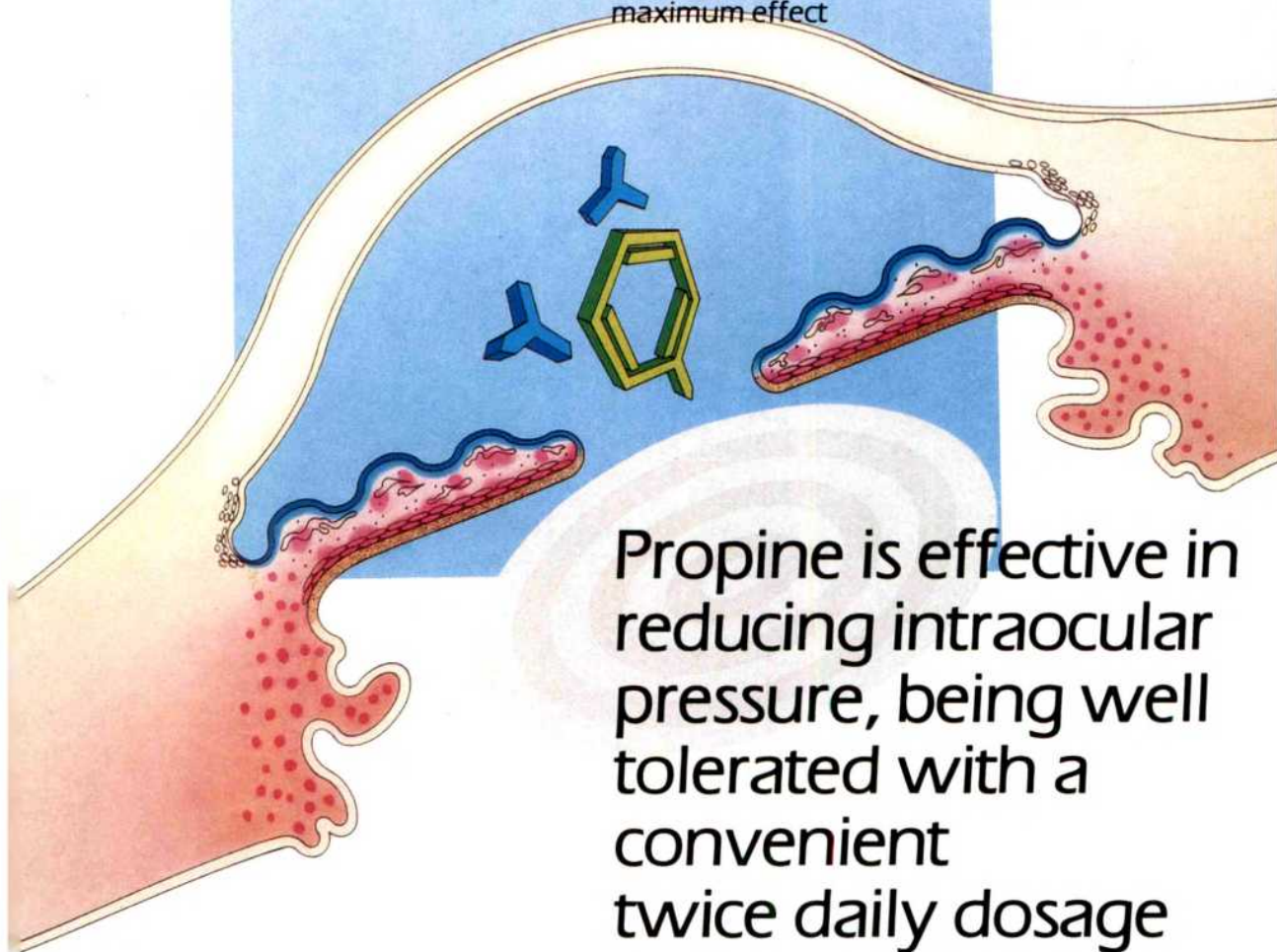
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A prospective study of histocompatibility testing for keratoplasty in high-risk patients

ÖZDEN ÖZDEMİR

From the Department of Ophthalmology, Ankara University School of Medicine, Turkey

SUMMARY Forty high-risk patients awaiting corneal grafting were randomly selected from a 7-year cumulative list. Twenty were grafted with HLA-A and HLA-B antigen matched material. The other 20 patients were used as controls. Graft survival at two years was 60% (12/20) in the control group and 90% (18/20) in the study group; at five years it was 55% (11/20) in the control group and 85% (17/20) in the study group.

In recent years corneal graft operations have become routine in the treatment of blindness caused by corneal trauma, oedema, inflammation, dystrophy, and congenital abnormalities that can result in opacification of the cornea. However, a significant percentage of grafts fail weeks to months after surgery. These are generally believed to be caused by immunomediated allograft rejection.¹

Several studies have shown that the rate of corneal graft rejection increases according to the degree of vascularisation of the cornea.^{2,3} Several retrospective studies have suggested that increased matching between HLA-A and HLA-B locus antigens yields improved corneal allograft survival,^{4,5} but some other studies have failed to confirm these findings.

This study gives the results after five years in 20 high-risk patients who had maximised HLA-A and HLA-B antigen matching and 20 high-risk control patients.

Patients and methods

This prospective study was started in Ankara University School of Medicine Eye Department between April 1978 and September 1979. Forty patients randomly chosen from the waiting list for a keratoplasty operation were identified as being at high risk of graft rejection by virtue of having significant vascularisation of one or more quadrants of corneal stroma or having had prior irreversible corneal allograft rejection.

These patients were divided into subgroups,

namely severe vascularisation involving four quadrants of the cornea, medium vascularisation involving two to three quadrants, and mild vascularisation of only one quadrant (Table 1). Thirty were male and 10 were female, and their ages were between 7 and 70 years.

All the patients had less than 0.1 (6/60) (Snellen) visual acuity before operation. They all had normal intraocular pressure, and none had ever had a blood transfusion, nor were they known to be sensitised with any material. But one patient had had a previous corneal allograft rejection.

The patients were tested before transplantation to identify their HLA-A and HLA-B genotype. Blood was taken from the donor's jugular vein 30-60 min after death; at the same time donor corneas were taken for the surgery.

HISTOCOMPATIBILITY TESTING

The standard microlymphocytotoxicity test was used for HLA serological typing of donors and recipients. We have used National Institute of Allergy and Infectious Disease Serum Bank material for the confirmation of antigen assignment. For the recognition of sera 14 HLA-A and 15 HLA-B specificities were used. The percentage of reactive antibody reflected the percentage of panel cells showing at

Table 1 Corneal vascularisation 20 controls and 20 cross matched patients

	Severe	Medium	Mild
Cross-matched	8	8	4
Controls	8	7	5

Correspondence to Dr Özden Özdemir, Çankaya Cad 69, Ankara, Turkey.

least 20% lysis by the patient's serum regardless of the method used.⁷

PRESERVATION OF CORNEAS AND TREATMENT

Donor corneas for patients in both study and prospective control groups were stored in McCarey Kaufman medium until keratoplasty. Surgery was performed within 50 hours of the donor's death. All donor buttons were punched from the posterior corneal surface on to a Teflon block with a trephine 0.5 mm larger than that used to incise the recipient bed. The standard surgical technique for penetrating keratoplasty was employed for all patients, with the use of interrupted 10-0 nylon sutures, approximately four sutures per quadrant.

After the operation topical steroids were applied two or four times a day for the first four weeks and then tapered over another four-week period. Most patients were maintained on one drop of topical steroid every day.

The sutures were removed when they loosened or if visible vessels encroached on the wound edge and began to migrate round the graft margin. Graft rejections were treated by hourly topical steroids and ointment once each evening. When severe inflammation was present, a periocular injection of 10 to 20 mg soluble dexamethasone was also given. Systemic steroids were withheld unless an extremely severe reaction was detected.

Results

The risk factors for all patients included in the study and in the retrospective control groups are listed in Table 2. No significant differences in age, sex, primary corneal disease, or vascularisation were seen between the groups. Most rejections occurred within nine months of transplantation in both groups.

The overall graft survival was 60% (12/20) for the control group and 90% (18/20) for the cross-matched group, with mean follow-up times of 24 months. The difference in survival was statistically significant (Fisher's exact test, $p < 0.03$).

The effect of HLA matching was examined for patients in the cross-matched group (Table 3). All rejections occurred in patients receiving poorly matched donor grafts. In the cross-matched patients of the severe vascularisation group only one rejected.

There was also one rejection from those who had medium vascularisation. There was a statistical difference in survival between the control group and the cross-matched group for severe and medium vascularisation, but no difference for the mild vascularisation groups (Table 4).

The effect of HLA antigen matching and pre-formed antibodies was examined for patients in the study and control group. Of the 20 patients in the study group 19 had a two locus HLA-A, HLA-B antigen match, and only one patient had a three locus antigen match. The patient who had a three locus antigen match had a severely vascularised leucoma. The vision was counting fingers before the operation. The graft was clear and vision restored to 0.4 after the operation. Only three patients had graft rejection in this study group (85%) (Table 5).

Of the 20 patients in the control group eight had had no antigen matching and 12 patients had had only one locus matching. The graft survived in five of those eight patients and in six of the 12. There was no

Table 2 Causes of corneal opacification

	Total	Control	Cases
Postinflammatory simple leucoma	27	14	13
Postinflammatory anterior synochiae	4	2	2
Viral infection	5	3	2
Burns	2	1	1
Previous graft	1	—	1
Corneal dystrophy	1	—	1

Table 3 Graft survival for 24 months

	Clear graft	Rejection	Total
Cross-matched	18 (90%)	2 (10%)	20
Controls	12 (60%)	8 (40%)	20

Table 4 Graft survival rate according to the vascularisation in 24 months

	Severe		Medium		Mild	
	Clear	Reject	Clear	Reject	Clear	Reject
Cross-matched	7	1	7	1	4	—
Controls	5	3	3	4	4	1

Table 5 HLA-A and HLA-B antigens

	No match		One locus match		Two locus match		Three locus match		Total
	Clear	Reject	Clear	Reject	Clear	Reject	Clear	Reject	
Cross-match	—	—	—	—	16	3	1	—	20
Controls	5	3	6	6	—	—	—	—	20

Table 6 Graft survival after five years

	Clear graft	Rejection	Total
Cross-matched	17 (85%)	3 (15%)	20
Controls	11 (55%)	9 (45%)	20

Table 7 Graft survival rate related to the preoperative vascularisation of the cornea: five years follow-up

	Severe		Medium		Mild	
	Clear	Reject	Clear	Reject	Clear	Reject
Cross-matched	6	2	7	1	4	—
Controls	4	4	3	4	4	1

statistically significant difference between these groups.

The overall survival of the graft at five years was 55% (11/20) for the control group and 85% (17/20) for the cross-matched group. The difference in survival was statistically significant (Fisher's exact test, $p < 0.05$).

The effect of HLA matching was examined for patients in the cross-matched group. All rejections occurred in patients receiving poorly matched donor grafts (Table 6). One further patient who had been cross-matched and who had severe vascularisation rejected his graft five years later. There was no difference between the medium and mild vascularisation groups at five years (Table 7).

Discussion

The results of this study indicate that donor corneal selection based on histocompatibility gives rise to a significant improvement in graft survival in patients who are at high risk of allograft rejection. Several recent studies have examined the role of HLA antigen compatibility in high-risk corneal transplant patients. Most of them include only a few cases and lack control groups. The difference in the overall graft survival between our control series (60%) and the previously reported 30–40%¹⁴ may be explained by improved surgical technique and follow-up. However, better donor selection provides a significant increase in graft survival for our cross-matched group, which was 90% in the 24 months mean follow-up period.

Transplantation of the avascular cornea differs significantly from that of a vascular graft, such as the kidney, but when the recipient cornea is vascularised the cornea may provide potential immune sensitivity. For this reason the allograft rejection rate is increased. This shows that the cornea has specific HLA

antigens just as other tissues have.⁴ The question of blood group antigens in the cornea remains controversial. The effect of blood group compatibility on corneal graft survival is unclear and probably minimal, even though blood group compatibility has been shown to affect renal transplantation.^{9,10}

This is the first prospective study of HLA typing in cases of corneal graft rejection among high-risk patients to be reported. All the retrospective studies also support the role of histocompatibility in patients at high risk of graft rejection, and, as reported by Ehler and Kissmeyer-Nielsen,¹⁴ the success rate is high. Another similar study by Foulks *et al.*¹⁵ showed a 95% rate for the study groups and 52% for control groups.

In this study graft survival was 55% (11/20) for the control group and 85% (17/20) for the cross-matched group at five years. Only one cross-matched patient with severe vascularisation rejected within this time. And in the control group the cases of graft rejection increased from eight to nine in the five years. Most of these rejections were in patients who had severe and medium vascularisation.

The extended preservation time obtained by the storage of the corneas in M-K media makes pre-operative testing possible. The increasing costs are at an acceptable level in an established transplantation testing laboratory.

According to this study higher graft survival rates, especially in high-risk patients, have resulted from the use of HLA-A and HLA-B matching for both the recipients and the donors.

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Hydrogel keratophakia: a freehand pocket dissection in the monkey model

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SUMMARY High water content hydrogels can be made with water and solute permeabilities comparable to those of the corneal stroma, thus making them feasible as intrastromal implants for refractive keratoplasty. The materials have been shown to be compatible with the cornea tissue, but for a lenticule of hydrogel to be effective in a refractive keratoplasty procedure it must alter the anterior curvature of the cornea. In this investigation hydrogel lenticules were implanted by a free-hand pocket dissection in eight *Macaca mulatta* (rhesus) and two *Macaca nemestrina* (pigtail) primate eyes. The results of pre- and postoperative keratometry and subjective retinoscopy as well as biomicroscopy were recorded. The alteration in refractive power was calculated in relation to the hydrogel lenticule parameters such as base curve, refractive index, etc. The corneal refractive change had a yield of $+3 \pm 27\%$ ($\pm$ SD). The central keratometric change had a yield of $+6 \pm 16\%$. The hydrogel plus power lenticule implanted in a free-hand intrastromal pocket created no significant steepening of the anterior cornea surface and therefore little change in refraction.

Refractive keratoplasty was introduced by Barraquer in 1949,¹ but recently interest in it has increased. The objective of the operation is to alter the anterior corneal curvature, providing a predictable, stable, and in some cases reversible change in refraction. Because of the large difference in the refractive indices of the precorneal tear film and air, small changes in the corneal radius will result in relatively large changes in its dioptric power. There are many types of refractive keratoplasty procedures, ranging from simple operations such as relaxing incisions and radial keratotomy to more complex, such as cryolathe keratophakia.

In 1966 Barraquer² placed alloplastic lenticules in the corneal stroma to achieve this goal. Successful implantation of different alloplastic lenses for therapeutic uses in corneal disease had been reported earlier.³⁻⁵ Alloplastic implants of glass and Plexiglass were insufficiently permeable to water and nutrients to maintain normal corneal physiology. Celloidin implants caused foreign body reactions resulting in neovascularisation of the cornea.³ Barraquer subse-

quently used human donor lenticules shaped on a cryolathe.⁴ In recent years hydrogel polymers have evolved into materials that have permeabilities comparable to that of the corneal stroma, making them feasible as intrastromal implants for refractive keratoplasty. For example, McCarey and Andrews⁷ used Permalens (Cooper Vision Laboratories, Inc.) as an aphakic intrastromal implant in keratophakia. The high water content hydrogels are well tolerated intralamellarily, eliciting no inflammation and minimal cicatricial response.⁸⁻¹⁰ McDonald *et al.*¹¹ performed three hydrogel implantations within intrastromal pockets. The postoperative keratometry indicated that the corneal curvature changed by 4% of the predicted dioptric increase. A definition of the predicted dioptric change was not given nor was a descriptive technique of assuring keratometric centration over the implant. In a second report from the same laboratory Koenig *et al.*¹² performed seven pocket implantations of hydrogel lenses followed by trephine keratotomy 1 mm peripheral and concentric to the implant. They found that despite the +14.00 dioptre power of the implant (power is defined for an air/hydrogel interface) there was no significant alteration in the anterior curvature of the cornea.

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The McDonald and Koenig reports indicate that the presence of Bowman's membrane in the primate eye prevents the pocket implantation of a hydrogel lens from creating an alteration in the corneal anterior curvature. These findings support Barraquer's earlier observations.

Because of the impact this surgical procedure could have and the lack of refraction data in the previous studies, we considered the topic warranted a careful re-evaluation in the non-human primate eye with long-term (approximately one-year) follow-up to check for delayed or progressive reshaping of the anterior stroma to the implant.

Material and methods

Ten hydrogel intracorneal lenses (ICL) were implanted in the corneal stroma of six adult *Macaca mulatta* (rhesus) and one *Macaca nemestrina* (pigtail) monkeys. The monkeys were anaesthetised intramuscularly with ketamine hydrochloride, 10 mg/kg body weight.

ICL PARAMETERS

The parameters of the ICLs that were implanted are listed in Table 1. There were six eyes with Sauflon (American Medical Optics), an 80% water content hydrogel, three eyes with Permalens (Cooper Vision Laboratories), a 70% water content hydrogel, and one eye with Vistamarc (Vistakon), a 58% water content hydrogel. The implant centre thickness was determined with the laboratory specular microscope by multiplying the measured thickness and the ratio of the refractive index of the hydrogel relative to the saline in which the ICL was immersed. The powers of the ICLs in air ranged from +8.00 to +16.00 dioptres as provided by the manufacturer from measurements in the hydrate state. While the edge thickness is an important variable in describing the ICL configuration, it is not easily measured in the laboratory. In order to define this parameter a hydrogel contact lens design analysis was performed as part of the main

data analysis programme referred to in the data analysis section.

SURGICAL PROCEDURE

A mid-depth 3 mm corneal incision was made 2 mm from and parallel to the superior limbus. When the stromal lamellae were sufficiently separated with a miniblade to form an intralamellar plane, a Martinez lamellar dissector was used to open a lamellar pocket large enough to centre the hydrogel intralamellar lens over the pupil. After completely forming the pocket, the incision entrance was enlarged with corneal scissors to allow the ICL to enter the pocket. The incision was closed with four to six interrupted 10-0 nylon sutures and the knots buried in the cornea peripheral to the ICL. Bacitracin-polymyxin ointment was applied topically.

PRE- AND POSTOPERATIVE EXAMINATIONS

The monkeys were anaesthetised intramuscularly with ketamine HCL (10 mg/kg). Cycloplegia was achieved with one drop of 1% cyclopentolate applied every five minutes for three doses one hour prior to retinoscopy. The examinations included biomicroscopy, pachymetry with a Haag-Streit I unit, central keratometry with a Bausch and Lomb keratometer, retinoscopy and corneal photography with a Zeiss photoslit lamp. The steepest and flattest keratometry readings were averaged to represent the central corneal curvature. The thicknesses of the anterior stroma, the hydrogel implant, the posterior stroma, and the combined components were recorded. The pachymetry data were used to determine the depth at which the implant lay. At each examination five pachymetry and keratometry measurements were taken and the mean computed as the representative value. Retinoscopy was performed by a single individual using trial lenses and was recorded as the spherical equivalent refraction.

DATA ANALYSIS

The measured refractive and keratometric changes

Table 1 Intrastromal hydrogel lens parameters

Monkey no.	Hydrogel	Power in air (D)	Base curve (mm)	Diameter (mm)	Measured centre thickness (mm)	Calculated edge thickness (mm)
MII 10/OD	Permalens	15.00	7.4	6.0	0.24	0.04
MII 10/OS	Permalens	15.00	7.4	6.0	0.24	0.03
NP80/OS	Permalens	14.50	7.4	6.0	0.29	0.09
P6/OD	Sauflon	10.00	6.4	6.4	0.24	0.07
P6/OS	Sauflon	10.50	6.2	6.4	0.23	0.10
RAM/OD	Sauflon	10.00	6.4	6.5	0.23	0.05
RAM/OS	Sauflon	8.00	6.4	6.5	0.22	0.08
MC82/OD	Sauflon	11.00	5.0	6.2	0.19	0.10
G1/OS	Sauflon	8.50	7.6	6.2	0.22	0.09
MC167/OD	Vistamarc	16.00	6.8	6.2	0.29	0.08

were compared with the expected or theoretical changes for the specific ICL and ocular parameters. An algorithm for the theoretical values was used to calculate the following variables: the corneal intralamellar bed radius, the new ICL diameter and anterior radius after altering the ICL base radius, and the postoperative corneal power including the effect of the refractive index of the ICL within the cornea. A complete discussion of the calculations is presented by Watsky *et al.*¹³ The measured keratometric and refractive changes created by the ICL were compared with the theoretically predicted values and expressed as the keratometry yield and refractive yield. For example, a 75% yield means the measured postoperative value is 75% of the theoretical value.

Results

The preoperative corneal measurements are listed in Table 2. The 10 monkeys had a mean spherical equivalent refraction of -0.41 ± 1.81 dioptres ($\pm$ SD), central keratometry readings of 51.38 ± 3.11 dioptres with a corresponding corneal radius of

6.56 ± 0.38 mm, and a central corneal thickness of 0.47 ± 0.04 mm.

After the postoperative follow-up period of 36 to 156 weeks biomicroscopy of the monkey eyes with ICLs showed: one eye with an intrastromal epithelial plaque, one with neovascularisation in the pocket, and three with debris in the pocket. The remaining six corneas were clear and quiet. Figure 1 illustrates the quiet appearance of the cornea 3.5 years after surgery. This animal continued to illustrate the biocompatibility of the hydrogel intracorneal implant even after 4.5 years.

The postoperative data are presented in Table 3. The average depth at which the implant was placed within the cornea was $74 \pm 10\%$, which was deeper than the desired 50%. The cornea refractive change had a yield of $+3 \pm 27\%$. The central keratometric change had a yield of $+6 \pm 16\%$. A perfect yield would have been $+100\%$.

Discussion

The tissue tolerance of the hydrogel was excellent, as indicated by the 3.5 year follow-up of two eyes with Permalens intrastromal implants (Fig. 1). However, the hydrogel plus power lenticule implanted in a free-hand intrastromal pocket created no significant steepening of the anterior corneal surface and therefore little change in refraction. The large standard deviations indicate poor predictability of this surgery. The main cause of the poor results is in the use of a pocket dissection in which the anterior collagen bundles and Bowman's layer are not severed; thus these structures resisted the anterior curvature change. Other variables included the animal model, manufacture of the ICL, and intrastromal bending of the ICL. The globe is an intact sphere consisting of collagen fibrils with limited short-term stretching characteristics. The ICL in the cornea increases total corneal thickness, and this

Table 2 Preoperative eye measurements

Monkey no	Refraction (spherical equivalent, dioptres)	Central keratometry (average dioptres)	Anterior corneal radius (mm)	Central corneal thickness (mm)
Mil 10/OD*	-3.75	47.54	7.10	0.50
Mil 10/OS*	-3.38	47.54	7.10	0.50
NP80/OS	-0.50	49.62	6.46	0.46
P6/OD	+0.87	52.80	6.39	0.41
P6/OS	+1.00	52.00	6.49	0.41
RAM/OD	-0.62	54.90	6.15	0.46
RAM/OS	+0.50	57.34	5.89	0.46
MC82/OD	+1.50	49.34	6.84	0.50
G1/OS	+0.75	51.06	6.61	0.45
M167/OD	-0.38	51.62	6.54	0.52

* *Macaca nemestrina*

Table 3 Results of placing high plus intrastromal hydrogel lenses in pocket incisions in the monkey cornea

Monkey no.	Follow-up (weeks)	Measured		Theoretical		(Measured-theoretical) $\times 100$		
		Dissection depth (%)	Change in refraction (dioptres)	Change in keratometry (dioptres)	Change in refraction (dioptres)	Change in keratometry (dioptres)	Refractive yield (%)	Keratometry yield (%)
MIL 10/OD	156	83	4.54	-0.43	11.48	10.64	40	-4
MIL 10/OS	156	86	5.59	-0.18	11.55	10.73	48	-2
NP80/OS	99	63	-3.30	4.71	11.07	10.57	-30	+4
P6/OD	55	66	-1.08	-0.53	7.12	7.55	-15	-7
P6/OS	55	75	-1.63	0.64	10.22	10.22	-17	6
RAM/OD	51	61	-0.91	0.82	6.85	7.35	-12	11
RAM/OS	51	72	1.16	-0.84	5.24	5.62	22	-15
MC82/OD	41	66	0.96	1.20	8.62	9.19	11	13
G1/OS	40	92	-1.17	0.52	5.98	6.12	-20	8
MC167/OD	36	79	0.40	0.80	12.63	10.83	3	1

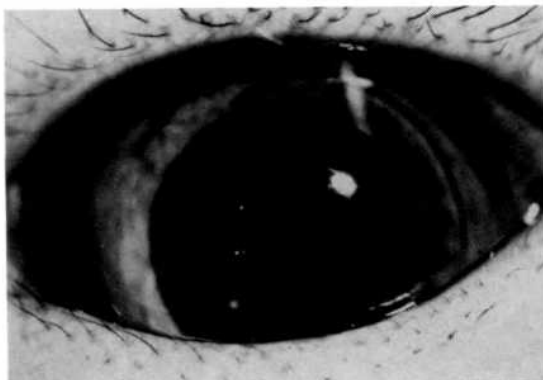


Fig. 1 The quiet clear cornea illustrates the biocompatibility of the Permalens implant within the cornea. The photograph was taken 156 weeks postoperatively of animal no. MIL 10/OD.

effect can be compared with the effect of oedema in the cornea. In both cases the lack of elasticity of the corneal collagen in Bowman's layer and the anterior stroma prevents the cornea from moving anteriorly (steepening) as it increases in thickness. One can think of the globe as being unable to increase its spherical size. The cornea increases its thickness only by expanding posteriorly (Fig. 2), a phenomenon that creates folds in Descemet's membrane and the posterior stroma as the thickness of the cornea increases and the arc distance from limbus to limbus decreases.

Problems in management of the monkeys makes evaluation of ICLs difficult. The postoperative



Fig. 2 The hydrogel implant within the pocket dissection creates a posterior bulging of the stroma. The photograph was taken 6½ months postoperatively of animal no. MC-82 with a Saufon material implant.

medication was limited because it could be administered only to a sedated animal, and frequent anaesthesia may disrupt the health of the animal. The difficulty in identifying the optical axis of the anaesthetised animal made refraction and keratometry less accurate.

An advantage of performing keratophakia with a hydrogel lenticule is the reproducibility in manufacturing the lenticule hydrogel. Unfortunately the small dimensions and high water content of the ICL make it difficult to lathe cut for the very steep monkey cornea. The average anterior corneal radius of the monkeys in this study was 6.56 mm (51.45 D). If the implant is located at 0.24 mm depth (about 50% thickness) in the cornea, the radii of the lamellar bed and the ICL base curve would be 6.39 mm. If the hydrogel being used contained approximately 70% water with a linear expansion factor of 1.6, then the manufacturer would have to cut the dehydrated hydrogel to a base radius of 3.94 mm. This small radius requires new technical skills for the manufacturer.

In order to create a predictable steepening or flattening of the anterior corneal surface, the anterior corneal collagen layers must be disrupted. One way to do this is to remove the anterior corneal lamellae, place a conformer or wedge such as the ICL on the lamellar bed, and then replace the anterior cornea so that it conforms to the curvature of the ICL, thus altering the anterior corneal surface. This is the approach used by Barraquer¹⁴ in keratophakia, and it may allow hydrogel keratophakia to be more effective and predictable.^{15,16} Another approach is to use intracorneal implants of a high refractive index material.¹⁷ This approach is attractive, since it can utilise the technically simple intralamellar pocket dissection. The implant itself can cause the refractive alteration without relying on subtle changes in anterior corneal curvature.

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Hydrogel keratophakia: a microkeratome dissection in the monkey model

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SUMMARY High water content intracorneal implants were fabricated from Vistamarc hydrogel (Vistacon, Inc.) at 58%, 68%, and 72% water content and a range of powers from +7.25 to +17.00 dioptres. The Barraquer microkeratome technique was used to implant the lens at $59.0 \pm 9\%$ ($\pm$ SD) depth in the corneas of 14 rhesus monkey eyes. The contralateral eye served as a control. Three eyes were lost to the study because of complications. The remaining 11 animals were followed up for 51 ± 2 weeks with the refractive yield being $118 \pm 34\%$ and the keratometric yield being $92 \pm 30\%$. The measured and theoretically expected refractive changes have a linear regression line correlation coefficient of 0.74, whereas the respective keratometric data had a correlation coefficient of 0.04. The measured refraction became stable within 2 to 3 dioptres after 20 postoperative weeks. The hydrogels were well tolerated within the corneal tissue. There was a minimum of interface problems except along the edge of the implant. Implants with abruptly cut edges versus a fine wedge tended to have more light scattering collagen at the implant margin.

Refractive keratoplasty with hydrogel implants has the potential to alter the anterior corneal curvature in the correction of either hypermetropia or myopia. The implants could be manufactured in limitless supply with well controlled parameters. Implanting high water content hydrogel lenses via a free-hand lamellar pocket dissection changes the refraction in rabbits¹ but not significantly in primate corneas.² Barraquer³ proposed to use the microkeratome to produce a lamellar dissection that would cut the relatively non-elastic collagen bundles and Bowman's layer. The lamellar disc can be contoured over the intrastromal lens, thus altering the anterior corneal surface curvature. Binder *et al.*⁴ found that hydrogel plus-power lenses implanted in a microkeratome incision could cause significant corneal topography steepening.

This paper reports the detailed results of hydrogel keratophakia by Barraquer's microkeratome technique in rhesus monkeys with lenses of three different water contents and various plus powers. The mean follow-up time of 12 months allowed evalu-

ation of the predictability of the procedure as well as correlation of the keratometric and refractive changes relative to the parameters of the hydrogel lenticule.

Materials and methods

INTRACORNEAL LENS PARAMETERS

The parameters of the intracorneal lenses (ICL) that were implanted are listed in Table 1. A total of 14 eyes received Vistamarc (Vistacon) lenses with water contents of 58% (six eyes), 68% (three eyes) and 72% (five eyes). The power (7.25 to +17.00 D), base curve (6.50 to 7.2 mm), and diameter (4.5 to 5.8 mm) of these lenses as indicated by the manufacturer were used in determining the theoretical refractions and keratometer values.² The manufacturer measured the hydrated lens power with a lensometer after blotting the surface water from the lens. It is difficult to measure the power of the hydrated lens while it is submerged in saline. The hydrogel has a refractive index too similar to that of saline to give a reliable reflex with the lensometer. Furthermore, the base curve cannot be verified by the projection method, because of the small diameter of the lenses. The edge

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Table 1 Preoperative data for 14 primate eyes undergoing intracorneal lens implantation

Primate	Corneal parameters			Intracorneal lens parameters					
	Keratometry reading (D)	Refraction* (spherical equivalent, D)	Thickness (mm)	ICL hydrogel, % water	Power (D)	Base curve (mm)	Thickness (mm)	Edge thickness† (mm)	Diameter (mm)
Z27F	51.37	-0.25	0.47	Vistamarc 58%	16.25	7.25	0.29	0.11	5.8
886F	52.60	+0.50	0.51	Vistamarc 58%	17.00	6.65	0.22	0.11	4.5
Y178	52.26	+0.63	0.44	Vistamarc 58%	14.75	6.65	0.25	0.16	4.5
834F	52.52	0.00	0.45	Vistamarc 58%	15.00	6.65	0.24	0.14	4.5
Y188	52.64	+1.88	0.49	Vistamarc 58%	14.75	6.65	0.22	0.14	4.5
Y4	51.48	-1.25	0.46	Vistamarc 58%	13.50	6.65	0.25	0.16	4.5
Y79	49.89	+1.00	0.46	Vistamarc 68%	10.00	6.50	0.18	0.10	4.7
N254	51.18	-3.13	0.47	Vistamarc 68%	8.00	6.51	0.21	0.14	4.9
MC173	51.10	+0.50	0.47	Vistamarc 68%	10.25	6.50	0.19	0.11	4.7
MC155	49.66	+0.25	0.48	Vistamarc 72%	14.25	6.65	0.22	0.10	4.7
575F	51.93	+0.50	0.41	Vistamarc 72%	12.25	6.50	0.20	0.10	4.8
3A	51.58	+1.00	0.46	Vistamarc 72%	13.50	6.50	0.20	0.10	4.9
Q522	49.19	+0.50	0.49	Vistamarc 72%	7.25	6.65	0.22	0.10	4.7
6019	52.45	+1.50	0.46	Vistamarc 72%	14.25	6.50	0.21	0.10	5.0

* Expressed as spectacle correction † Calculated by an algorithm.

thickness was predicted by means of an algorithm described by Watsky *et al.*⁵ The laboratory specular microscope was used to measure the thickness of the implants.

SURGICAL PROCEDURE

Fourteen hydrogel intracorneal lenses (ICLs) were implanted in the corneal stroma of 14 adult rhesus monkeys (*Macaca mulatta*) of both sexes (Table 1). The animals were anaesthetised with intramuscular ketamine HCl (10 mg/kg) with supplements of 5 mg/kg intravenously. After facial cleaning with providone-iodine solution the animal was placed in a supine position with the head in a stereotactic clamp and an adhesive plastic drape over the face. The plastic drape was cut open over the eye to be operated upon with the opening large enough to minimise interference with the movement of the microkeratome head. A 360° peritomy exposed the bare sclera so that the suction ring would adhere firmly. A lateral canthotomy with total mobilisation of the lateral canthal ligament was necessary to allow placement of the microkeratome on the globe. A

needle-scratch reference mark was made at 12 o'clock in the corneal epithelium to allow accurate realignment of the corneal lamellar disc. The eye was proptosed by a retrobulbar injection of 2 ml of balanced salt solution to give access for the microkeratome.

The 10-9 paediatric suction ring of the Barraquer microkeratome (Steinway Instruments, San Diego) was placed on the bare sclera with the conjunctiva retracted. The desired 40 mmHg intraocular pressure was confirmed with the microkeratome applanation unit. The diameter of the lamellar disc to be removed was checked with the 8.5 mm calibrated sizing applanator. The thickness of the lamellar disc was theoretically set to be 0.35 mm with a baseplate no. 35 inserted in the microkeratome head along with a new blade for each eye. The microkeratome cut was made with a smooth sweeping movement. The suction was released immediately after the cut and never exceeded 90 seconds in duration. The lamellar disc of the cornea was replaced in its original position guided by the epithelial reference mark at the 12 o'clock position. The area was carefully irrigated,

and three cardinal 10-0 nylon sutures were placed and tied at the nasal, 12, and 6 o'clock positions. The temporal suture was put in place and the intracorneal lens inserted from the temporal side after repeat irrigation of the lamellar bed. The ICL was carefully centred and the fourth cardinal suture tied. Sixteen interrupted 10-0 nylon sutures were used in preference to a running suture, so that selected sutures could be removed to reduce neovascularisation or irritation caused by a loose, disrupted suture. After all the sutures were tied, corneal curvature was measured with a Schmirmaul quantitative keratometer mounted on the operating microscope. High astigmatism was corrected by replacing or adjusting the tension of one or two tight sutures. All knots were buried on the peripheral side of the wound. The ICLs central location within the lamellar bed was secured by one 10-0 nylon suture through the anterior stroma and the margin of the ICL at the 12 o'clock position. In practice it was noted that the monkey could dislocate the unsecured ICL during the early postoperative period by rubbing its eye.

The lateral canthotomy was closed with one suture and the conjunctiva was repositioned on to the limbus. Atropine 1% solution and polymyxin B-bacitracin-neomycin ointment were instilled at the end of the procedure. 1 ml of saline was injected subcutaneously in the upper eyelid to cover the globe and protected it from rubbing during the immediate postoperative period. The monkeys were treated with intramuscular injections of the non-steroidal anti-inflammatory drug flurixin meglumine (Benamine), 1 mg/kg twice daily for three to five days.

PRE- AND POSTOPERATIVE EXAMINATIONS

Pre-examination anaesthesia and cycloplegia were

performed as described by McCarey *et al.*² The examination included slit-lamp microscopy, central pachymetry with the Haag-Streit I unit, central keratometry, retinoscopy, and slit-lamp photography. All monkeys had at least one preoperative examination. Postoperative examinations were performed on the 3rd and 7th, 14th and 21st days after surgery, monthly for six months, and then bimonthly. During the immediate postoperative period the animals had a partial examination (that is, biomicroscopy and, if possible, estimated pachymetry and keratometry) on the 3rd and 7th postoperative day as well as removal of loose sutures. The suture through the ICL was removed on the 7th postoperative day. After three weeks all remaining sutures were removed. The retinoscopy data reported in this manuscript (except for Figs. 2 and 3) are the average value from the last three examinations and are expressed as the spectacle correction. The theoretical change in refraction was calculated by means of an algorithm developed by Watsky *et al.*³

Results

POPULATION STUDIED

The preoperative corneal measurements of the 14 corneas (Table 1) showed central keratometry readings averaged 51.40 ± 1.12 D ($\pm$ SD) or radius 6.57 ± 0.15 mm, spherical equivalent refractions averaged 0.26 ± 1.23 D, and central corneal thickness averaged 0.46 ± 0.02 mm.

Three monkeys were omitted from the postoperative refractive results. Animal Z27 developed a corneal ulcer and the ICL was removed at week 12. One animal, 886F, died of aspiration pneumonia at week 18. Severe corneal vascularisation developed in response to fierce eye rubbing by animal 6019, and the ICL was removed at week 24. The results of the remaining 11 animals are presented with follow-ups ranging from 49 to 53 weeks.

PACHYMETRY

The preoperative full corneal thickness for the 11 eyes averaged 0.46 ± 0.02 mm ($\pm$ SD). After approximately one year of postoperative follow-up the same set of eyes minus the implant thicknesses averaged 0.54 ± 0.02 mm. Pachymetry showed increasing thickness postoperatively in both operated and contralateral unoperated eyes. In five out of 10 animals the experimental cornea was significantly (*t* test, $p < 0.005$) thicker than the control cornea. No animals showed a significant decrease of total stromal thickness following implantation of a hydrogel lens. Since the implant separated the anterior and posterior lamellae, the postoperative values include two subjective pachymetry endpoint decisions. The thickness of the

Table 2 Postoperative pachymetry* of primate eyes with hydrogel intracorneal lenses

Primate	Anterior plus posterior (mm)	Anterior lamellae (mm)	Depth of ICL in cornea (%)†
Y178	0.50	0.25	50
834F	0.52	0.24	46
Y188	0.57	0.36	63
Y4	0.55	0.42	76
Y79	0.53	0.31	58
N254	0.56	0.30	54
MC173	0.56	0.30	54
MC155	0.57	0.39	68
575F	0.53	0.31	58
3A	0.53	0.36	68
Q522	0.55	0.31	56

* Average of last three examinations.

† Anterior lamella thickness divided by anterior plus posterior lamella thickness.

Table 3 Postoperative data for 11 primate eyes with hydrogel intracorneal implants

Primate	Week postoperative	Refractive change*			Keratometry			
		ICL power (D)	Theoretical (D)	Measured† (D)	Yield (%)	Theoretical (D)	Measured* (D)	Yield (%)
Y178	52	14.75	12.20	13.13±1.34	108±11	10.57	9.07±1.50	86±15
834F	51	12.50	12.31	12.49±1.67	101±14	10.76	6.94±3.16	64±29
Y188	52	10.50	11.94	10.63±0.42	89±4	10.11	6.83±0.32	67±4
Y4	48	13.50	10.94	9.18±0.55	86±6	9.09	4.35±0.39	48±4
Y79	52	10.00	7.79	7.85±1.71	100±22	7.76	6.85±0.45	92±6
N254	52	8.00	6.40	8.32±0.44	125±14	6.22	8.19±0.97	131±15
MC173	53	10.25	7.88	9.93±1.02	127±13	7.57	9.41±1.66	124±22
MC155	53	14.25	5.91	9.06±0.95	153±16	5.78	6.58±0.35	114±5
575F	49	11.25	9.39	11.37±0.63	121±6	9.13	6.81±0.12	75±1
3A	52	13.50	10.35	9.75±0.44	94±4	9.96	7.83±0.45	79±5
Q522	51	7.25	5.21	10.46±0.23	201±3	5.30	7.23±0.63	136±10

* Expressed as spectacle correction † Average of last three examinations

anterior lamellae excised with the no. 35 microkeratome base plate should be 0.35 mm, but it measured an average of 0.32 ± 0.06 mm (mean±SD) (Table 2). The depth of the implant in the cornea averaged $59 \pm 9\%$ (mean±SD) relative to its postoperative thickness (anterior+posterior lamellae).

CHANGES IN CORNEAL POWER AND REFRACTION

The postoperative data in Table 3 contain the theoretical and refractive changes as well as the measured change in refraction and keratometry (average of the last three examinations) for 11 animals. The average postoperative follow-up was 51 ± 2 weeks with the refractive yield being $118 \pm 34\%$ and the keratometric yield being $92 \pm 30\%$. The measured versus theoretical expected refractive changes had a linear regression line correlation coefficient of 0.74, whereas the respective keratometric data had a correlation coefficient of 0.04. The measured refractive changes of each animal was graphed for the 51 week follow-up (Figs. 1 and 2). The measured refraction became stable within 2 to 3 dioptres after 20 weeks. When data from the same animal group were graphed by the refractive yields (Fig. 3), a greater spread was shown. Although many animals had yields between 80 and 120% after 20 weeks, some of the higher water content lenses resulted in much higher yields (Fig. 4).

SLIT-LAMP MICROSCOPY

The hydrogel ICLs were tolerated well within the corneas of the animals. Most animals showed a slight grey lining at the implant margin. Hydrogel lenses with an abruptly cut edge instead of a rounded, tapered, or buffed edge tended to have more of this build-up. At the interface of the ICL and the stroma refractile particles could be detected in some animals. At the site of the microkeratome cut scarring to some

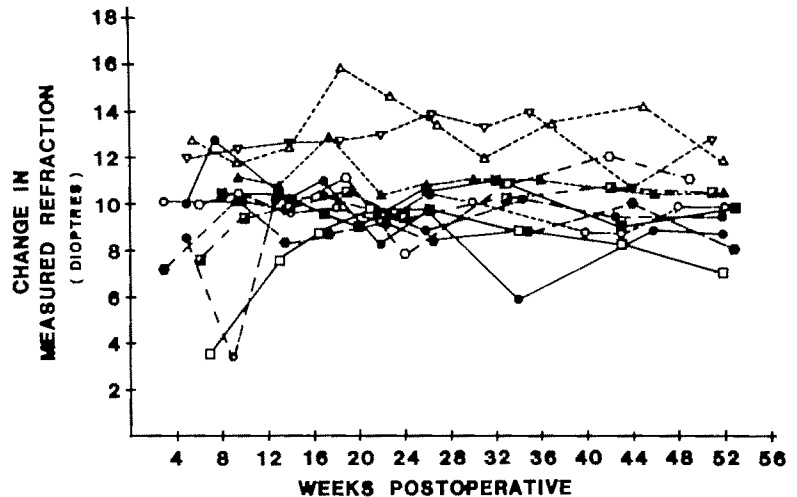
extent was present in all animals. Epithelial down-growth into the bed of the microkeratome cut did not occur in any of the animals. Animal Z27 was removed from the study at 12 weeks postoperatively because an ulcer developed at the margin of the implant. The implant was removed and subsequently the cornea became clear. After 24 weeks of observation the

PRIMATE #	SYMBOL
Y178	△
834F	▽
Y188	▲
Y4	○
Y79	●
N254	□
MC173	■
MC155	◇
575F	◆
3A	⊙
Q522	⊠

HYDROGEL WATER CONTENT	
58%	-----
68%	_____
72%	-----

Fig. 1 Key of symbols used in Figs. 2, 3, and 4.

Fig. 2 Long-term follow-up of the changes in the measured refractions relative to the preoperative refractions illustrates the stability of the corneal/hydrogel implant complex. Symbols as in Fig. 1.



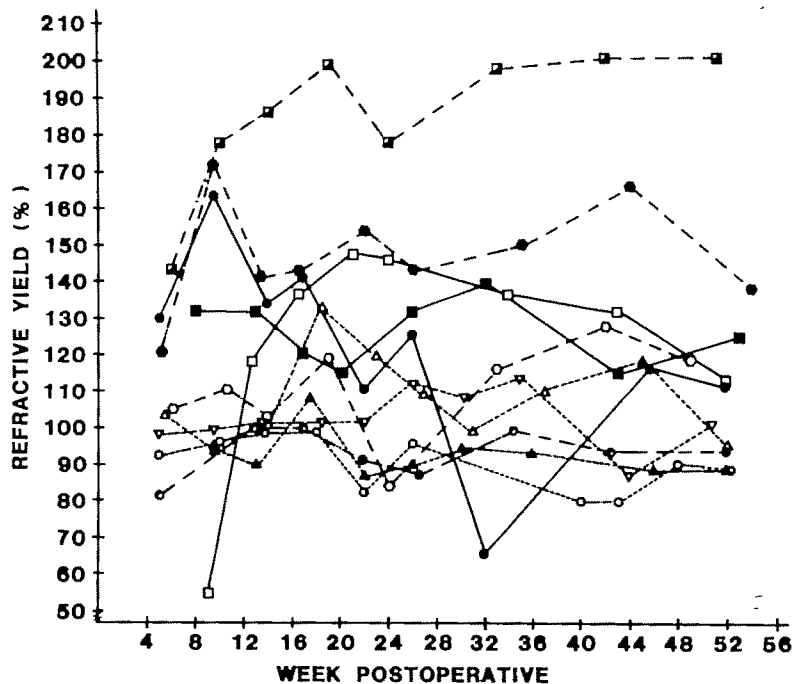
implant was removed from the cornea of animal 6019. There was marked vascularisation and more than average scarring because this animal was rubbing his eye in an unusually fierce manner during the past surgical period.

Discussion

Since the monkey eye dimensions and facial structure are different from those in man, we had to adjust the

Barraquer microkeratome technique. We found it necessary to use the paediatric microkeratome ring with a 360° conjunctival peritomy, a lateral canthotomy, and a retrobulbar injection of saline in order to gain exposure to the cornea and adequately to secure the microkeratome suction ring. Even then a smooth path of the microkeratome was sometimes impeded by orbital and nasal structures. After surgery the monkey's propensity to rub the irritated eye was only somewhat reduced by a saline injection to expand the

Fig. 3 When the long-term data are graphed by the calculated refractive yield (measured refractive change divided by the theoretical change) the data appears to have an unacceptably excessive spread. Symbols as in Fig. 1.



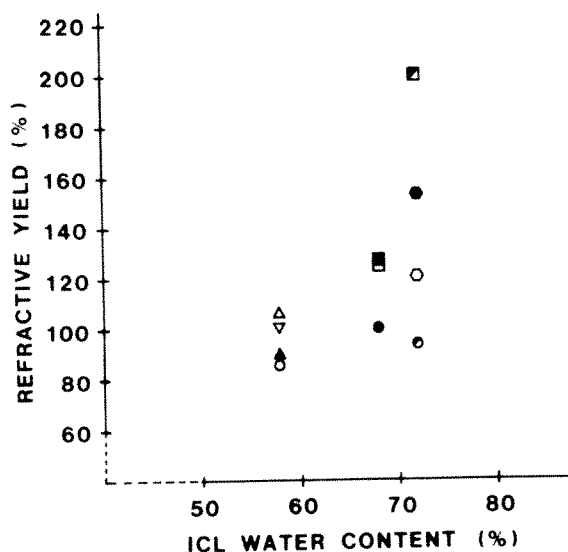


Fig. 4 Summary of the refractive yields (measured refractive change divided by the theoretical change) relative to the water content of the hydrogel implant illustrates the increasing variability with increasing water contents which helps to explain the spread in Fig. 2. Symbols as in Fig. 1.

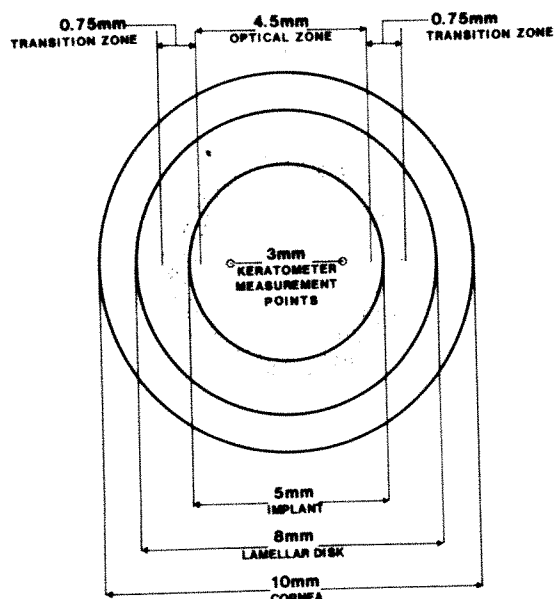


Fig. 5 The corneal curvature measurement by Bausch and Lomb keratometer is taken at two points on a circle with a diameter of 2.8 to 3.1 mm. The estimated irregular transition zone at the edge of the ICL is represented as a dotted area. The keratometry readings should be centred over the ICL, which is very difficult to see, since even slight decentration will cause false readings in the transition zone.

upper lid over the globe and frequent examinations to remove the irritating loose sutures.

The keratometry measurements are difficult on monkeys because of the optical principles of the instrument in combination with the animal model. The Bausch and Lomb keratometer with the addition of a +1.25 D auxiliary lens to extend the instrument's dioptric range measures the corneal curvature from points on a 2.8 to 3.1 mm circle (the range depending on the radius of curvature), (Fig. 5). The anaesthetised monkey cannot fixate on the central light of the keratometer, and therefore the exact surface location being measured is unknown. The ICLs have diameters of approximately 5 mm, with the optical zone being approximately 4.5 mm. If the keratometry is not precisely centred over the implant, which cannot be visualised through the keratometer, there will be a large variation of the readings. This is illustrated by the poor correlation between expected and measured keratometry values. Keratoscope photographs have the same problem of centration.

Hydrogel ICL implantation in lamellar pockets in primate eyes does not change the corneal surface curvature² as it does in rabbits.¹ A microkeratome dissection is necessary to allow the hydrogel implant to be placed between smooth surfaces in the corneal stroma at a level of even depth. Dissecting the anterior stromal lamella free from the cornea and placing it over the hydrogel lenticule results in the outer surface conforming to a predictable curvature. When a lenticule (positive or negative power) is introduced in the stroma to change the anterior corneal curvature, the arc length on the corneal surface will increase. The anterior stromal layers, including Bowman's layers of the primate eye, are not elastic as in the rabbit eye. These layers will not stretch to a larger arc length over an implanted wedge.

The relationship between the water content of the implanted lenticules and the yield of refractive change was examined (Fig. 4). The 58% water content lenticules have the best predictability (yields close to 100%). The 68% and 72% water content lenticules have less ideal yields. We think these differences are due to: (1) errors in the calculation of the expansion factor, and (2) variation of hydration of the materials by the manufacturer. Neither the hydration of each lot of lenses nor the refractive power was double checked in this study prior to implantation, for reasons explained above and in an earlier paper.² Another cause for differences in results between materials with various water contents might be a change in dimension, that is, hydration, of the hydrogel material within the corneal stroma due to mechanical compression or stromal swelling pressure. These factors have been considered in a sep-

arate study.⁶ The conclusion of that study was that hydrogel materials up to a water content of 70% can be considered stable within the corneal stroma. Materials of higher water content undergo a hydration decrease by a few percent when exposed to physiological swelling pressures. This observation does not, however, explain the higher yields found in this study for the higher water content Vistamarc materials.

Pachymetric measurements have shown that the anterior lamellae are thinner than the intended 0.35 mm that would be expected with the microkeratome fitted with the no. 35 base plate (Table 2). This may be explained by the earlier observations that the hydration of the stroma anterior to the ICL decreases.¹

In analysis of our pachymetric data we have considered mainly the difference between the stromal thickness of the experimental eye and the control eye at each measuring point. Both the experimental corneal thickness and the control values increased significantly in thickness over time. Subtracting the two values at each time point illustrated that half the experimental group was significantly greater than the control eye and the other half was statistically equal to the control. The increase in the control thickness over time can be ascribed to either age changes in the animal or measurement error, of which the latter is probably the most important factor. The retinoscopic reflex did not deteriorate during the follow-up period.

In conclusion, the implanted hydrogel materials were well tolerated in the primate corneal stroma; 11 out of 14 implants have been technically successful. The refractive change was stable after ICL implantation. The measured refractive change correlated well with the calculated refractive change in most animals, but the higher water content hydrogel implants gave less predictable results. Keratometry was an unreliable measure of the change in corneal power in this experimental primate study.

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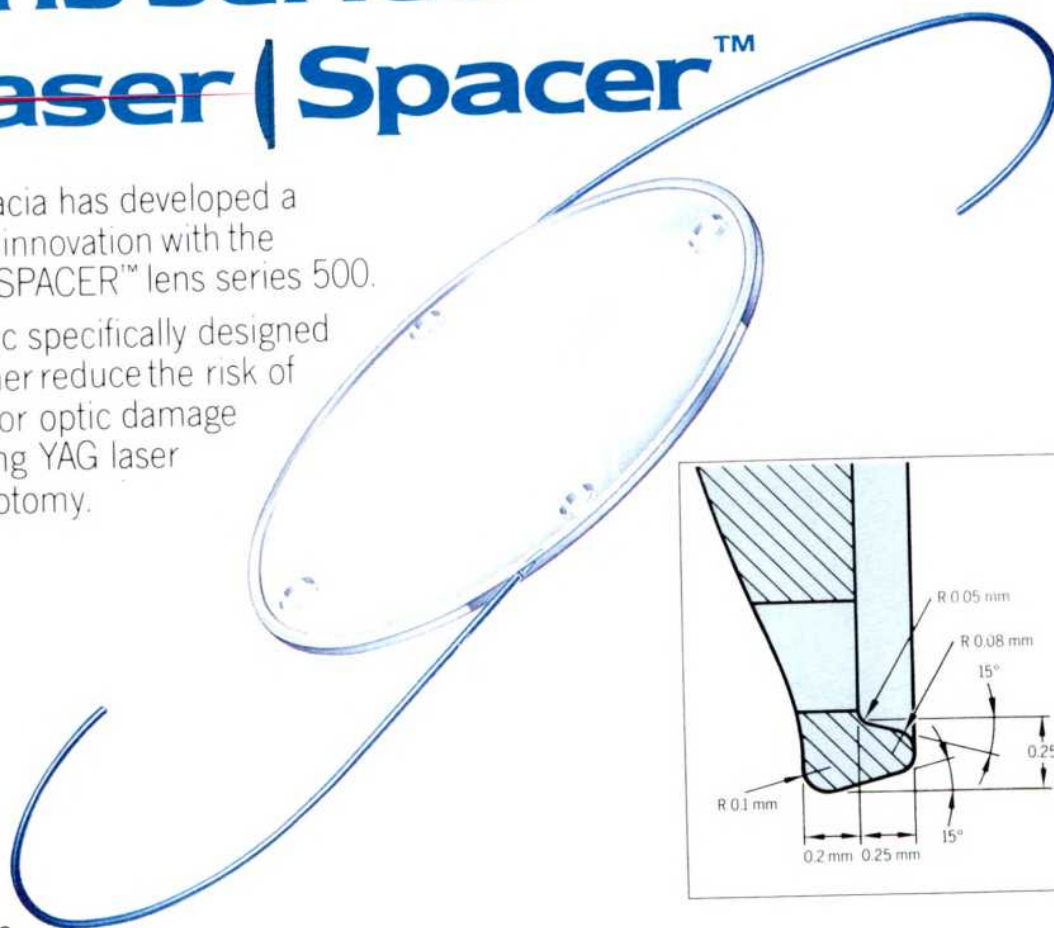
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Management of bacterial corneal ulcers

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SUMMARY A prospective microbiological study of 48 patients with corneal ulcers due to bacterial infection was performed. Positive cultures of corneal ulcer samples were obtained in 60% of all patients; about half of these patients had received antimicrobial treatment prior to sampling. A relatively high incidence of *Staphylococcus epidermidis* was isolated from ulcer patients (27%) compared with normal controls (10%). Gram stains of ulcer samples were positive for organisms in only 27% of all patients and were not considered useful in determining initial therapy in this series. We concluded that treatment should be started with a broad combination of antibiotics while awaiting the culture results.

Despite the easy access of the cornea to therapeutic agents the treatment of bacterial corneal ulcers remains a problem. There are basically two approaches to the management. The specific therapy advocated by Jones¹ is most widely accepted and is based on the examination of corneal scrapings with culture identification of the offending organism and treatment of the ulcer according to its antibiotic sensitivity. Alternatively the broad therapy developed by Baum² is based on the prevalence of organisms known to produce disease in a particular geographic location. A broader treatment regimen according to the known sensitivities of the most likely organisms is given.

Both approaches require a knowledge of the causative organisms and their sensitivities. This paper presents the findings of a microbiological study of patients with bacterial corneal ulcers referred to Groote Schuur Hospital for treatment. Peripheral staphylococcal ulcers have been specifically excluded from the study.

Patients and methods

During the period January 1983 to March 1984, 48 patients were seen at Groote Schuur Hospital with clinically diagnosed bacterial corneal ulcers. All cases of uninfected erosions, viral keratitis, fungal keratitis, and peripheral staphylococcal infection have been excluded from this study. Patients' ages ranged

between 8 and 80 years with an average of 50 years; 69% were males and 31% females.

On admission of the patients to hospital corneal samples were taken for Gram stain and culture. The cornea was anaesthetised with 0.4% oxybuprocaine solution without preservative (Minims Benoxinate). In each case samples were taken from the base and leading edge of the ulcer by means of sterile calcium alginate swabs,³ care being taken to avoid touching the conjunctiva and lids. The material was spread over a localised area on pre-cleaned glass slides for immediate Gram stain and microscopic examination. Further samples were taken for direct inoculation into cooked meat medium, boiled blood agar, and Sabouraud's agar for culture identification of organisms. Corneal and conjunctival swabs were taken for similar Gram stain and culture from 39 control patients with clinically uninfected eyes admitted for routine surgery such as lens extraction and squint correction.

Our treatment regimen followed that advocated by other authors.^{1,2} The initial treatment was based on the results of the corneal smears. All patients received 1% atropine drops twice daily. Gram-positive cocci were treated with subconjunctival cephamandole and hourly topical 10% cephamandole drops, and Gram-negative bacilli were treated with subconjunctival gentamicin and hourly topical 3% gentamicin drops. If no organism was identified both cephamandole and gentamicin were used. The subsequent management of all ulcers was determined by the culture and sensitivity results as well as the clinical response to treatment.

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Results

GRAM STAIN RESULTS

Pus cells were present on the smears taken from 38 patients (79%). However, in all the remaining patients who showed no pus cells on the smear there was clinical evidence of infective keratitis, with a frank hypopyon in all but one of these cases. Organisms were identified on the smears taken from 13 patients (27%), seven patients showing Gram-positive cocci and six Gram-negative bacilli.

CULTURE RESULTS

Positive corneal cultures were obtained from 29 patients (60%). Gram-positive cocci were most commonly isolated, but Gram-negative bacilli and mixed bacterial ulcers were also identified (Table 1). Fifteen of these patients had received antibiotic therapy (chloramphenicol 14; neosporin 1) for a variable period before being referred to us and, therefore, before their corneal smears were taken for culture.

Of the 19 patients with negative corneal cultures eight had received antimicrobial therapy before being referred to us and culturing (chloramphenicol

Table 3 Organisms isolated from 39 control patients

Organism	Number of isolates	
	Conjunctive (%)	Cornea (%)
No organisms	33	87
<i>Staph. epidermidis</i>	49	10
<i>Staph. aureus</i>	13	0
<i>Bacillus</i> species	5	3

5; framycetin 1; tobramycin 1; sulphacetamide 1).

Of the 13 patients with positive Gram stains organisms were cultured from nine; eight of these were appropriate to the Gram stain and the other one was different from what the Gram stain showed (Table 2). From the remaining four patients no organisms were cultured.

Although we cultured organisms from 60% of patients, not all positive cultures were necessarily significant. There was a relatively high incidence of *Staphylococcus epidermidis* (27% of all patients), which is a normal resident of conjunctiva and lids.⁴ To clarify the role of *Staph. epidermidis* we took corneal and conjunctival swabs from 39 control patients with clinically uninfected eyes admitted for routine surgery.

NORMAL CONTROLS

Organisms were isolated from 67% of conjunctival swabs but only 13% of corneal swabs taken from the same eye of 39 control patients (Table 3). There was a high incidence of *Staph. epidermidis* cultured from the conjunctival swabs, thus confirming its residential status in the conjunctiva. Most of the corneal organisms cultured were also *Staph. epidermidis*; in all cases the organisms cultured from the corneal swabs were also found in the conjunctival cultures, indicating that these organisms were present in the pre-corneal tear film.

Discussion

The successful management of bacterial corneal ulcers is based on prompt identification of the causative organism and effective treatment with an appropriate antibiotic.^{1,5} Unfortunately the Gram stain and culture results are not always positive. We cultured organisms from 60% of patients with corneal ulcers, and this compares favourably with the results of other authors, who have reported incidences of positive cultures ranging between 53% and 73%.^{4,6}

A number of factors may influence the culture results. Usually only a small amount of material is available, giving a light growth of organisms. Topical anaesthetic agents are known to have antimicrobial

Table 1 Organisms cultured from corneal ulcers

Organism	Number of isolates	Prior therapy*
Gram-positive cocci:	20	12
<i>Staph. aureus</i>	4	2
<i>Staph. epidermidis</i>	9	6
<i>Str. pneumoniae</i>	6	3
<i>Str. viridans</i>	1	1
Gram-negative bacilli:	5	1
<i>Pseudomonas aeruginosa</i>	3	1
<i>Moraxella</i> species	1	—
<i>Haemophilus influenzae</i>	1	—
Mixed infections	4	2
<i>Staph. epidermidis</i> /diphtheroids	4	2

*See text for details

Table 2 Gram stain and culture correlation

Gram stain	Culture	No patients
Gram and culture correspond (8 patients)		
Gram-positive cocci	<i>Str. pneumoniae</i>	2
	<i>Staph. epidermidis</i>	2
Gram-negative bacilli	<i>Pseudomonas aeruginosa</i>	2
	<i>Moraxella</i> species	1
	<i>Haemophilus influenzae</i>	1
Gram and culture different (5 patients)		
Gram-positive cocci	No growth	3
Gram-negative bacilli:	No growth	1
	<i>Str. viridans</i>	1

activity and their use may lead to false negative culture results.⁸ We instilled preservative-free Minims Benoxinate immediately before taking samples for culture, as it does not interfere significantly with the isolation of organisms from corneas.⁹ This made the sampling procedure more comfortable for our patients, enabling us to obtain adequate samples without touching the lids or conjunctiva.

Treatment of ulcers with antibiotics prior to corneal culturing may also reduce the number of positive results. Almost half (23 patients) of all our corneal ulcer patients received topical antibiotics before smears were taken for culture. However, it is significant that about half of the patients with positive cultures had been treated with antibiotics prior to culturing. Thus previous treatment does not necessarily preclude positive culture results and should not be a reason for avoiding sampling.

In this study we have followed the type of regimen advocated by Jones¹ in which the initial therapy was based on the results of the Gram stain and treatment was subsequently adjusted according to the culture and sensitivity results. Our Gram stain results were disappointing because organisms were identified in only 27% of all patients, and subsequent culture confirmed the identity of these organisms in only 57% of these patients. The Gram stain was therefore not very useful in determining the appropriate initial therapy in our series. In one patient a different organism was cultured. On the Jones regimen this patient received inappropriate medication until the time that the culture report was available. Since it often takes 48 hours before the culture results are known, we now prefer to ignore the Gram stain and start treatment with a broader combination regimen while awaiting the culture results.³ Treatment may subsequently be modified according to the sensitivity of the organism as well as the patient's response to treatment.

A relatively high incidence of *Staph. epidermidis* was isolated from our corneal ulcer patients (27%). This organism is a normal resident of conjunctiva and lids,⁴ and its role in ocular disease has been the subject of much controversy recently.^{7,10} It is known to be pathogenic in some immunologically compromised patients.¹¹⁻¹³ We found that in all normal control cases with positive corneal cultures the same organism was isolated from the conjunctival cultures from the same eye. These organisms were therefore present in the precorneal tear film and could either colonise or contaminate an area of corneal ulceration

sufficiently to be detected on the corneal culture.¹ Unfortunately this does not answer the question of the pathogenicity of *Staph. epidermidis*. However, it may be pertinent that a higher incidence of *Staph. epidermidis* was cultured from the patients with corneal ulcers (27%) than from the normal controls (10%). This suggests that some of these ulcers were due to exogenous *Staph. epidermidis* or alternatively that patients having this organism resident are more prone to infection. Mahajan *et al.*^{7,12} have shown that approximately one-third of isolates of *Staph. epidermidis* taken from various types of ocular infections showed dermonecrotic activity and were therefore regarded as pathogenic. Although *Staph. epidermidis* may not be of importance in all ulcers, it cannot be disregarded, and it would seem prudent to treat such an infection actively.

We thank Professor A A Forder for encouragement and guidance and Miss B Robinson for microbiological assistance.

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Oxybuprocaine keratopathy: a preventable disease

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SUMMARY Topically applied anaesthetics may lead to a serious keratopathy. Three patients presented to us with disciform keratitis, peripheral corneal ring, and stromal infiltration following the topical use of oxybuprocaine. All three patients developed marked decrease in vision secondary to corneal scarring. In all three patients oxybuprocaine was dispensed over the counter by a pharmacist. Legislation for the restriction of over-the-counter sale of topical anaesthetics, steroids, and antibiotics is essential in the prevention of many of the self-induced ocular disorders seen in developing countries.

Topical anaesthetics are commonly used by ophthalmologists for minor procedures and ocular examinations. The adverse side effects of their longterm topical use have been previously reported.^{1,2} Fuchs¹ showed that intensive use of topical anaesthetics produced severe changes in the corneal epithelium and delayed recovery from corneal diseases.

The indiscriminate use of topical eye drops, the lack of control of prescription drugs, and the availability of over-the-counter topical anaesthetic eye drops are common factors in the predisposition to abuse of topical anaesthetics in developing countries. We present here three cases of oxybuprocaine keratopathy.

Case reports

CASE 1

A 42-year-old Saudi male presented with a history of pain, photophobia, and redness of the eyes for two days. He had sustained a welding arc flash injury three days earlier, and a pharmacist gave him a bottle of oxybuprocaine 0.4% (Novesin), which he used every half-hour without ophthalmological surveillance. On examination he was found to have a visual acuity of 20/200 in each eye. A large central epithelial defect was noted in each eye. Oxybuprocaine was discontinued and both eyes were patched.

Despite the discontinuation of the topical anaesthetic the patient persisted in having corneal epithelial

defects and developed corneal oedema and a sub-epithelial peripheral ring infiltrate. He was admitted to hospital and put on topical dexamethasone 0.05% eye drops without preservative to both eyes every three hours and topical atropine 1% eye drops once daily.

The corneal epithelial defects showed slow but progressive improvement and evidence of re-epithelialisation. The peripheral corneal ring infiltrate persisted in the left eye and partially resolved in the right eye (Fig. 1). The patient was discharged from hospital, and over the next six days the right corneal epithelial defect healed, leaving residual stromal oedema. The left cornea showed a central corneal ulcer, and corneal scrapings contained *Staphylococcus epidermidis*. Steroids were discontinued and the ulcer responded to topical antibiotics. His final best corrected vision was counting fingers at 5 feet (1.5 m) in the right eye and 20/80 in the left eye.

CASE 2

A 39-year-old Saudi male presented with a history of foreign body in the left eye. He had gone to a pharmacy where he received a bottle of oxybuprocaine 0.4% (Novesin). He instilled the eye drops in the left eye once every hour. On examination his vision was 20/25 in the right eye and 20/100 in the left. The right eye was normal. The left eye showed conjunctival injection. There was a central epithelial defect involving approximately one-third of the corneal surface with superficial stromal infiltration near the limbus at 5 o'clock (Fig. 2). The anterior chamber showed no cells or flare. Gram stain showed occasional polymorphonuclear cells but no organisms.

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Fig. 1 Left eye of a 42-year-old male with self-induced oxybuprocaine keratopathy showing epithelial defect and 360° peripheral ring infiltrate.

The patient was treated with oral analgesics and topical balanced salt solution eye drops every two hours, 2% homatropine twice daily, and 0.5% chloramphenicol four times daily. The epithelial defect healed and the stromal infiltrate resolved. Two weeks later he presented with diffuse epithelial oedema and two areas of elevated bullae. Healing was associated with superficial corneal scarring, and his final best corrected vision was 20/100.

CASE 3

A 42-year-old Saudi male was admitted with a history of excruciating photophobia, and redness in both eyes of one week's duration. After being exposed to a welding arc flash for a period of one and a half hours he used topical oxybuprocaine 0.4% (Novesin) once every hour for a period of four days.

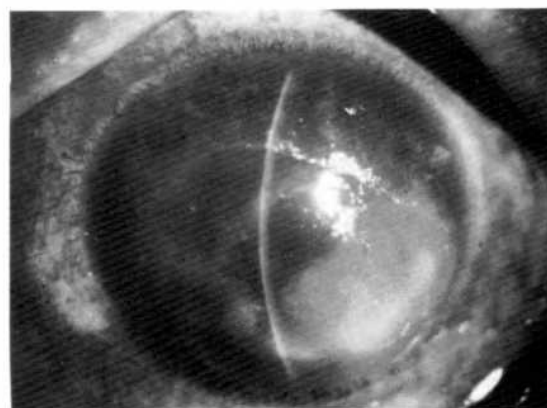


Fig. 2 Large central epithelial defect with severe stromal infiltration in a patient with self-induced oxybuprocaine keratopathy.

On examination the patient was found to have a visual acuity of counting fingers at 3 feet (1 m) in each eye. Biomicroscopy revealed bilateral corneal oedema, with peripheral ring infiltrates and 360° pannus. The anterior chamber reaction could not be assessed.

He was given gentamicin ointment to both eyes twice daily and homatropine 2% eye drops twice daily. Culture of corneal scrapings was negative. Dexamethasone 0.05% (without preservatives) four times daily was added to the therapeutic regimen.

The corneal peripheral infiltrates subsided and the epithelial and stromal oedema resolved in two weeks. Four days after healing he developed a large central epithelial defect in the right cornea that healed over the next six days. Diffuse superficial corneal scarring and vascularisation were noted, and his final acuity was 20/100 in both eyes.

Discussion

Loss of corneal epithelium and stromal opacity resulting from acute or chronic overuse of topical anaesthetics have been previously reported.²⁻⁶

Klima and Ruckerova² reported on a patient receiving long-term topical applications of 0.4% oxybuprocaine (Novesin) who developed severe degenerative keratopathy with total shedding of the epithelium associated with oedema, haziness, and neovascularisation of the stroma, striae in Descemet's membrane, and decrease in vision. Henkes and Waubke⁷ reported on three patients with severe keratitis resulting from the abuse of topical anaesthetics (oxybuprocaine, Novesin). Two of the three patients presented with centrally located epithelial erosion, stromal infiltration, and keratitic precipitates. One patient who continued to use oxybuprocaine (Novesin) for six weeks developed contact dermatitis of the skin of the eyelid. A large corneal epithelial defect, stromal oedema, and superficial and deep vascularisation were noted. The patient also had a mild anterior uveitis.

Several mechanisms could be involved in the pathogenesis of the keratopathy. A slowly developing eczematous contact dermatitis of the eyelids and nearby skin suggests a delayed hypersensitivity reaction.⁴

The toxic effects of topical anaesthetics on the corneal cellular metabolism lead to depressed cellular respiration and glycolysis and to accumulation of lactic acid. Ultrastructural alterations in desmosomes, intracellular proteins, and cell membrane permeability have been reported following the use of topical anaesthetics. Inhibition of cell mitosis and migration were demonstrated by Smelser and Ozanics,⁸ causing delay in healing of corneal epithelium.

Three topical anaesthetics are commonly used, namely, proparacaine, tetracaine, and benoxinate or oxybuprocaine. They are considered to be of low cellular toxicity, and there is no clinically significant difference in potency among them.⁹ It is interesting to note that most of the previously reported cases of topical anaesthetic keratopathy were due to the misuse of oxybuprocaine or benoxinate, and not to proparacaine or tetracaine.^{2-4, 10} All three of our cases had received oxybuprocaine. Oxybuprocaine is a para-aminobenzoic acid ester. Used topically in the eye it has a duration of anaesthetic action similar to that of tetracaine, 28 minutes.⁹ The majority of topical anaesthetics have preservatives, and Novesin has chlorhexidin 0.01% as a preservative.

When the anaesthetic diffuses deep into the stroma, it may inhibit the cellular metabolism of the keratocytes and posterior layers of the cornea. Inhibition of the endothelial cell metabolism may lead to corneal oedema.⁸ Weekers,⁶ in a study of the influence of cocaine, lidocaine, and benoxinate on the corneal epithelium of rabbits, concluded that the topical anaesthetic caused alteration of the Na⁺/K⁺ endothelium pump, resulting in increased osmotic pressure in the cornea and subsequent increased hydration of the stroma. The anaesthetic may penetrate to the anterior chamber, exerting its toxic effects on intraocular structures.^{4, 11, 12}

Loss of corneal sensation would decrease the blinking reflex and predispose the corneal surface to further desiccation. Prolonged use of anaesthetic may damage the corneal nerves and lead to neurotrophic ulcers.^{4, 11}

We strongly believe that visual loss from the abuse of topical anaesthetics can be prevented by restricting over-the-counter dispensing of topical medications in certain developing countries as happens in Saudi Arabia.

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Slit-lamp measurement of the anterior chamber depth

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SUMMARY A technique is proposed which allows assessment of the anterior chamber depth with a standard table slit-lamp without any extra attachments. A final approximation is made which suggests that a 1° change in the angle between the observation and illumination systems of the slit lamp when the end point is reached indicates a change in anterior chamber depth of 0.1 mm.

The first recorded slit-lamp technique for measuring the depth of the anterior chamber was that used by Donders in 1872. In this technique the slit-lamp is focused on the corneal endothelium and then the anterior lens surface. The slit-lamp movement between these two positions gives the apparent depth of the anterior chamber. In 1914 Ulbrich utilised the Donders technique with the additional refinement of a micrometer drum to measure the slit-lamp movement accurately. The technique, of course, relies on the eye maintaining a fixed position during the time that the slit-lamp is moved from the endothelium to the anterior lens. This is a major drawback of the technique. Increased accuracy was claimed by Lindstedt,¹ who employed a spherical and a cylindrical lens to produce an astigmatic bundle of light rays. The spherical lens was focused on to the cornea and the cylindrical lens was moved until its power meridian focused on to the anterior lens. This allows a simultaneous comparison of the two images, and the lens positions are used to deduce the anterior chamber depth. The technique was further improved by Stenstrom² with the addition of Scheiner discs to the optical system.

At present the commonest technique applied is that which uses parallel sided glass plates to displace half the image of an optical section until the corneal endothelium of one half coincides with the anterior lenticular surface of the other. Jaeger³ developed this approach, and it is employed in present-day pachometers. The pachometer has proved to be a rapid, convenient, and accurate method of estimating anterior chamber depth. But there is a need to have some means of recording the anterior chamber depth without recourse to expensive and sometimes in-

compatible accessories for the slit-lamp. Jacobs⁴ proposed a method of measuring the anterior chamber depth with a standard Haag-Streit 900 slit-lamp. In this method the microscope is fixed at a 45° angle to the illumination system. A slit is projected on to the patient's cornea, and the patient is instructed to fixate the slit. The slit is then focused on the anterior lens surface with its inferior edge coincident with the centre of the pupil. The out-of-focus slit image on the cornea is then observed and its length adjusted until the slit length appears to be equal to the gap between the corneal endothelium and the anterior lens capsule as observed in the optical section. The method was applied to 56 eyes of 28 consecutive patients and compared with results obtained with the Haag-Streit pachometer. The equation deduced for predicting anterior chamber depth was

$$x = \frac{(y + 0.21)}{0.78},$$

where y = slit length and x is the anterior chamber depth according to the pachometer measurement. The correlation between the two sets of results was 0.98. The above relationship was converted to an approximate clinical relationship of anterior chamber depth = slit length $\times 1.4$ and this was said to be accurate to 95% confidence limits over the range of chamber depths encountered. It was claimed that a depth estimate accuracy of ± 0.2 mm relative to standard pachometry could be achieved.

Smith⁵ also suggested a method of anterior chamber depth measurement, again using the Haag-Streit 900 slit-lamp and its calibrated adjustable slit length facility. The technique utilises a horizontal slit with the angle between the observation and illumination system set at 60°. The patient is instructed to fixate the biomicroscope with the illumination system in the patient's temporal field, and the slit is focused

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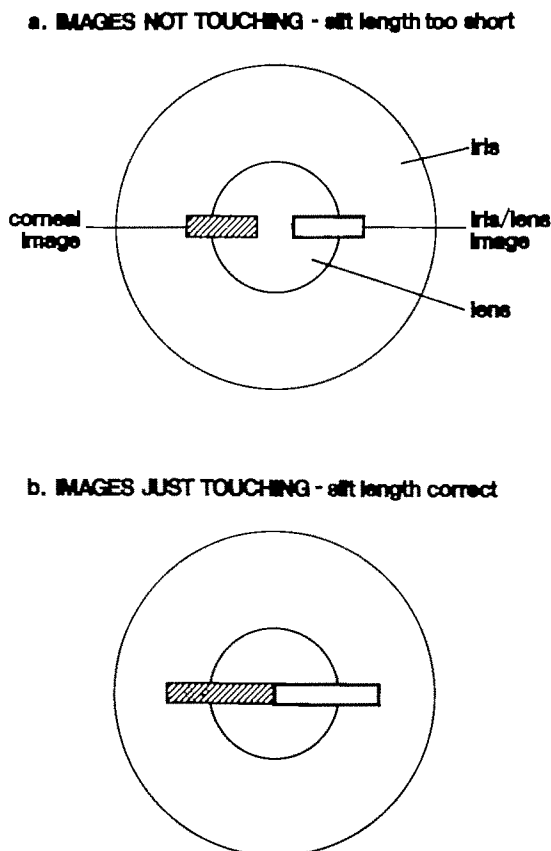


Fig. 1 Observer's view of slit-lamp images on cornea and iris/lens when using the method suggested by Smith.⁵

on the patient's cornea. The observer's view is illustrated in Fig. 1. The optical system is illustrated (in simplified form) in Fig. 2. As the slit length is increased, the gap between the cornea and lenticular slits decreases until the corneal slit appears to be just touching the lenticular slit. Smith recorded the slit length when this end point was reached and compared the result with the pachometric measurement of anterior chamber depth. Once again a high correlation of 0.966 was noted between slit length and pachometric depth measurement. The linear relationship between the two was deduced as $y = 1.117x + 0.5079$, where x = slit length and y is the pachometric depth measurement. The correspondence subsequent to the publication of Smith's paper revealed an earlier attempt at anterior chamber depth measurement by Gorbani⁴ using a similar approach to the problem. The previous techniques provide for anterior chamber depth estimation without the need for special accessories. However, they require a slit-lamp with a calibrated variable slit

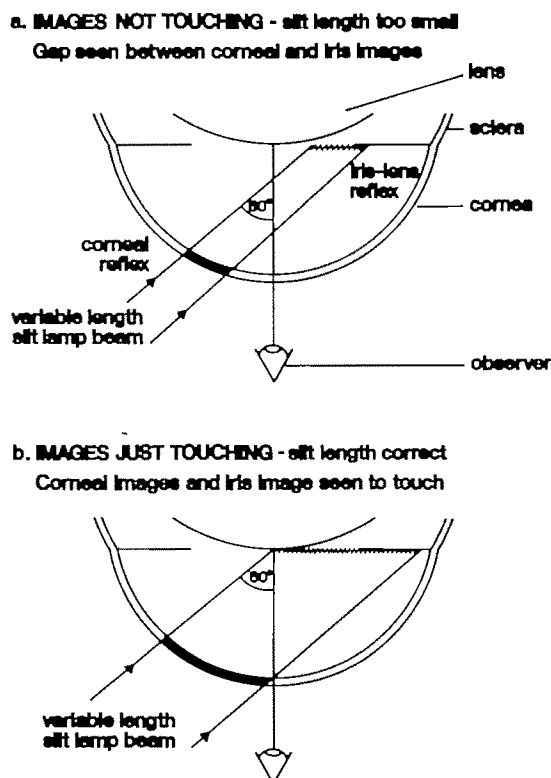


Fig. 2 Simplified optical diagrams of the slit beam traversing the anterior chamber in Smith's method.

length. It was believed that a modification of Smith's technique could provide a method for use with any slit-lamp.

Method

It was decided to follow the example of Jacobs⁴ and Smith⁵ and measure the anterior chamber depth with the Haag-Streit pachometer to obtain a reliable indication of chamber depth in each subject. The pachometer was used following the recommendations of Lowe⁷ with two exceptions. Firstly, six measurements of chamber depth were taken and averaged. Secondly, a small piece of frosted Perspex was placed above the slit diaphragm. The patient was instructed to fixate the slit aperture so that the light fell on the corneal apex. The reflected light will produce an out-of-focus slit image on the Perspex screen, and this was aligned with the slit diaphragm by lateral adjustment of the slit-lamp position. This ensures that the same central section of the anterior eye was observed when the measurement was repeated.

The arrangement originally utilised for anterior

chamber depth measurement without the pachometer was similar to that illustrated in Fig. 2 and involved the subject fixating the biomicroscope with the slit focused on to the cornea at an illumination system angle of about 80° to the observation system. However, considerable difficulty was encountered in making observations, mainly owing to corneal reflections. The difficulties were minimised by interchanging the observation and illumination systems.

The method finally adopted was as follows. A horizontal slit of 2 mm length (obtained by using the aperture diaphragm disc) and approximately 0.5 mm width was projected on to the eye with the subject fixating the slit diaphragm. This small bright target is an aid to steady fixation, and the fixed position of the illumination system ensures that a depth measurement of the central region including the corneal apex is made in every subject independent of anterior chamber depth. The slit was centred in the pupillary aperture and was then adjusted until the corneal and lenticular slits appeared to have the same vertical dimension. Thus both images were slightly out of focus, with the true focus of the slit lying between the posterior cornea and anterior lens. The objective magnification was set at $1\times$ with a $10\times$ eyepiece. The observer viewed the anterior eye using the biomicroscope eyepiece nearest the illumination system at an angle of about 80° on the temporal side. The observer's view at this point is similar to that illustrated in Fig. 1a. The angle between the observation and illumination systems was then reduced by moving the microscope until the temporal edge of the corneal slit appeared to be just touching the nasal edge of the lenticular slit as in Fig. 1b. The angle between the two systems was noted by means of the protractor scale on the slit-lamp main column. The angle can be estimated to the nearest 0.5° if the Vernier scale is used. Six measurements were made on each eye and a mean calculated.

If it is assumed that the corneal and lenticular slits are formed in a plane and are separated by an anterior chamber depth d of refractive index 1.336, then

$$d = \frac{2}{\tan \left\{ \sin^{-1} \left(\frac{\sin \theta}{1.336} \right) \right\}}$$

where θ = angle between the observation and illumination systems. This is perhaps an oversimplification and may lead to some inaccuracy.

Results

Fifty eyes were examined in subjects with ages ranging from 19 to 57 years; six pachometric and six angular measurements were taken on each eye. The standard deviation of each set of six results was

deduced in order to assess the likely variation in measurement. The mean standard deviation for the 50 eyes was 0.03 mm by pachometry and 0.04 mm by angular measurement. The mean and median depth for the 50 eyes were very similar, suggesting that the group is a normally distributed sample. The equation illustrated at the end of the method was used to deduce the anterior chamber depth. This correlated very well with the chamber depth measured by pachometer. Since the correlation coefficient was very high ($r=0.95$), a linear regression equation was deduced to compare the depths predicted by both methods. The angular measurement gives a depth estimation which is 0.3 mm less than that indicated by the pachometer. This illustrates the inaccuracy arising from the equation used to deduce anterior chamber depth, which it will be recalled makes certain assumptions to simplify the mathematical treatment. A correction factor of 0.3 mm could be added to the depth calculated in order to give a more realistic result.

In clinical work it would be more convenient to use a simple table that converts the angular measurement into an anterior chamber depth. This can be derived

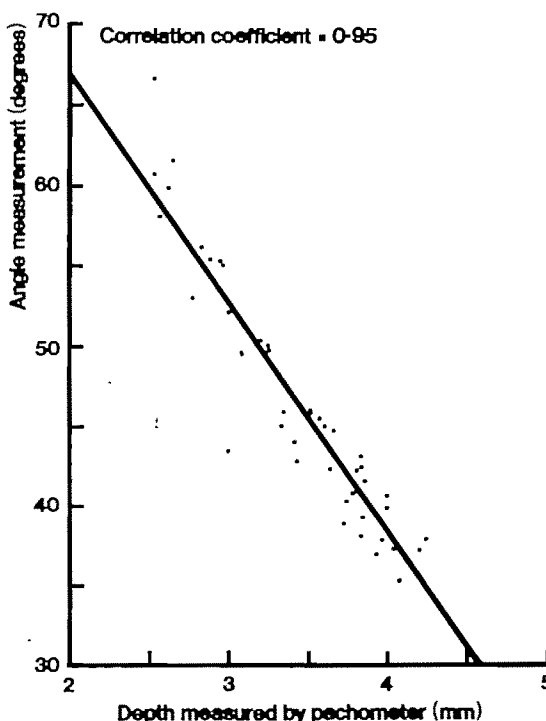


Fig. 3 Graph of anterior chamber depth measured by pachometer compared with the angular measurement between the observation and illumination systems of the slit-lamp following a modification of Smith's method.

Table 1 Angle to anterior chamber depth conversion. This table was derived from the regression line illustrated in Fig. 3

Angle °	Depth, mm	Angle °	Depth, mm
35	4.22	49	3.24
36	4.15	50	3.17
37	4.08	51	3.11
38	4.01	52	3.04
39	3.94	53	2.97
40	3.87	54	2.90
41	3.80	55	2.83
42	3.73	56	2.76
43	3.66	57	2.69
44	3.59	58	2.62
45	3.52	59	2.55
46	3.45	60	2.48
47	3.38	61	2.40
48	3.31	62	2.34

following the example of Jacobs⁴ and Smith⁵ by analysing the angular measurement and the pachometry depth that accompanies it. Fig. 3 illustrates the relationship. The points on the graph mark the measurements taken. The relationship appears to be approximately linear over the range of chamber depths encountered in this work. The line on the graph is the linear regression line obtained by the least squares method and is of the form $y = 14.35x + 95.56$, where y is the angle between the observation and illumination systems and x is the chamber depth indicated by the pachometer. This regression line is deduced on the assumption that the pachometer depth measurement is less likely to suffer from errors than the angular measurement. Once again the correlation coefficient is high at 0.95, and so this regression can be used to deduce a table comparing angular measurement with expected chamber depth. Table 1 illustrates the relationship, which indicates that a 1 degree change of angle is required for a 0.07 mm change in depth over an angular range from 35° to 62° (depth range 4.22 to 2.34 mm). Since the geometry of the system

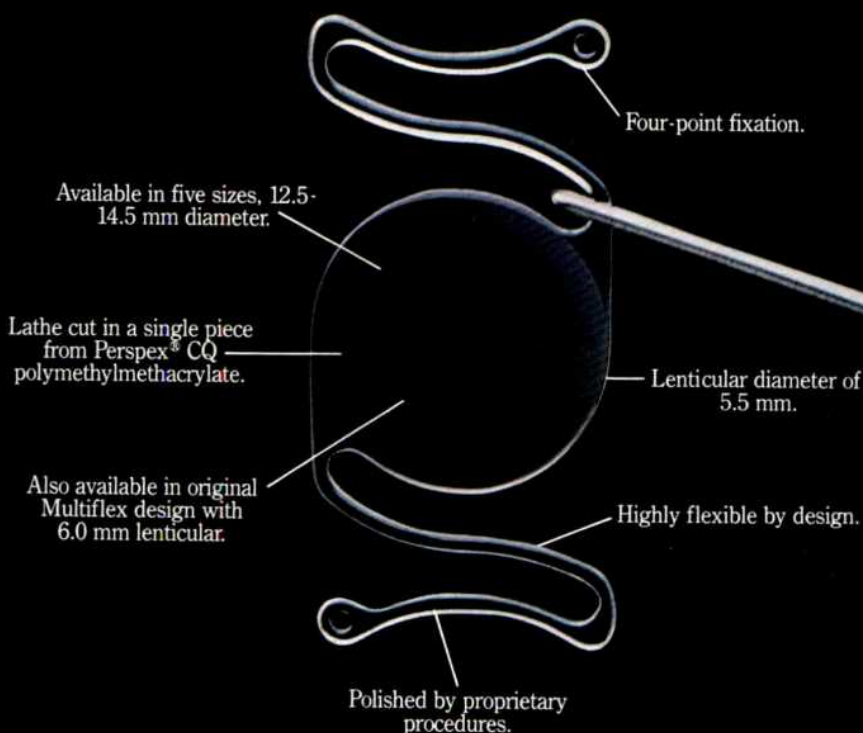
indicates that the relationship is not strictly linear, absolute depth predictions outside the range of values encountered in this study must be viewed with caution until the range is extended by examining more subjects, particularly with shallow anterior chambers. However, ray tracing by accurate calculation using the constants of Gullstrand's exact eye suggests that, for an anterior chamber depth of 1.5 mm, the error induced by extrapolation of Table 1 results in an overestimation of chamber depth by 0.05 mm. The calculations also suggest that total internal reflections will occur at the anterior corneal surface for a chamber depth around 1 mm, which sets the lower limit for the technique. It may be appropriate to round the chamber depth values in Table 1 to the first decimal place. This approximation suggests that a 0.1 mm change in chamber depth will be accompanied by a 1° change in the angle between the observation and illumination systems. This approximation is not only easily remembered but compares favourably with the approximations of Jacobs⁴ and Smith.⁵

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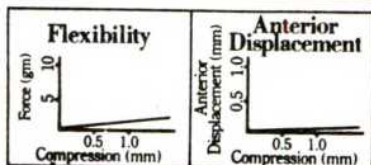
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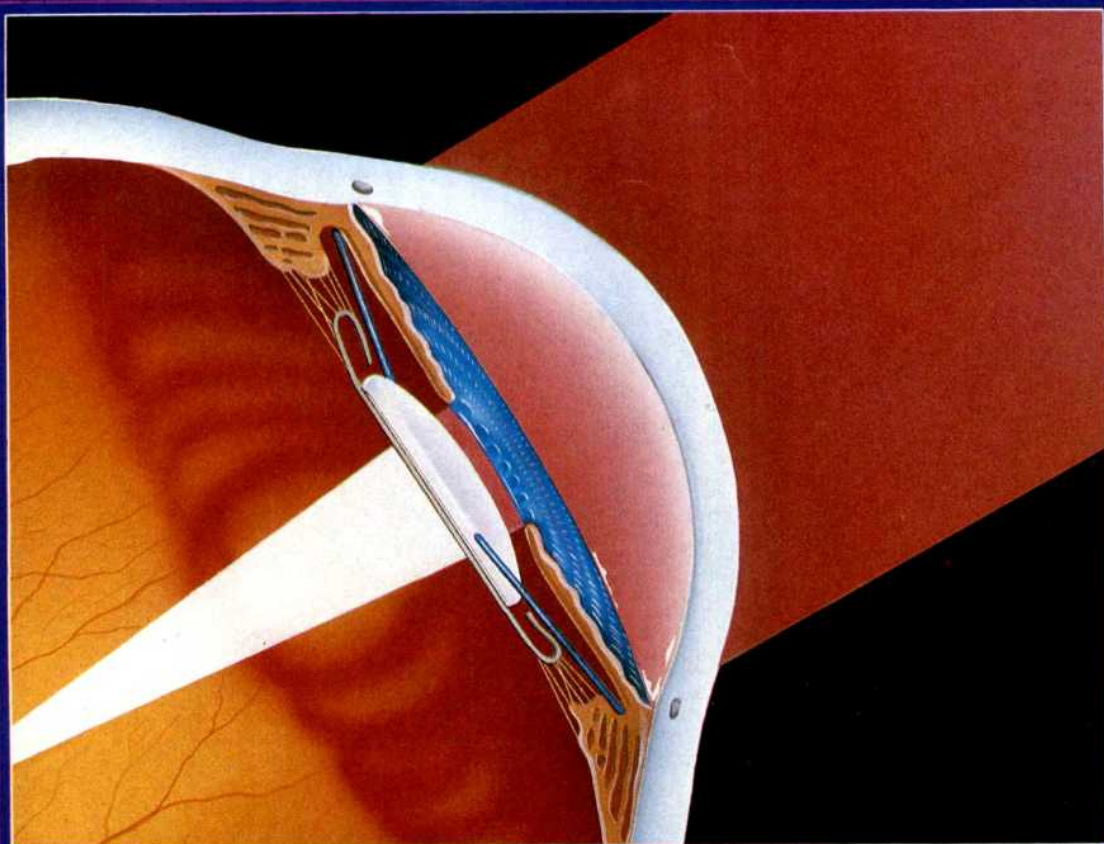
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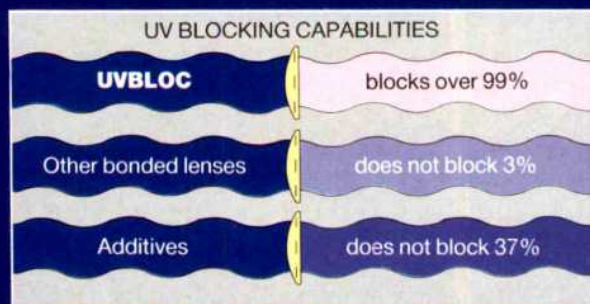
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Macular dazzling test on normal subjects

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SUMMARY The macular dazzling test was performed on 240 healthy eyes, classified into six groups according to the ages of the subjects. The test was used to assess both long distance and short distance vision with a simultaneous study of the influence of mydriasis and miosis.

The MDT is a test easy to perform, requires a minimum of co-operation by the subject, and gives repeatable results. The MDT values increase significantly as the age of the subject increases. The sex of the subject has no influence on it, and there are no significant differences between a subject's right and left eyes. Mydriasis does not affect the MDT, but miosis reduces the recovery period. All the values are statistically greater for long distance vision than for short distance vision.

One of the methods for the subjective exploration of the retina (visual acuity, Amsler table, static perimetry, colour vision) is the Bailliant test.¹ This test was formulated to determine the functional macular reaction by dazzling the retina and then measuring the length of time which the subject takes to regain the level of visual acuity he had prior to the dazzling. Since what is actually being explored with this method is the function of the macula, we refer to it as the macular dazzling test (MDT). One of the characteristics of the test is the use of induced macular fatigue, like the induced fatigue used for heart studies.²

The purpose of the work reported here was to standardise the MDT technique and thus to typify the results for normal subjects, not only for long distance vision—as previous authors have done—but also for short distance vision, in addition to studying the influence of the diameter of the pupil on obtaining results.

Materials and methods

We have performed the MDT on 240 healthy eyes. The ages of the subjects ranged from 10 to 69 years, the ratio of the sexes being 50:50. The subjects were divided into age groups as follows: from 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 to 69 years. Each age group contained 20 subjects, 10 male and 10

female. In all cases their visual acuity was equal to or greater than 20/25, with or without optical adjustment, and we accepted a refraction defect of not more than 3 dioptres of hypermetropia, myopia, or astigmatism.

To produce the dazzle, a Minolta electronic flash, guide no. 20 in meters with 100 ASA, with a 1/2000s flash, was used. A Heuer chronometer was used to measure the recovery time for visual acuity following the dazzling.

Long distance visual acuity was explored through the use of Snellen optotypes and short distance vision by means of the Parinaud test. To perform the MDT we followed the method proposed by Lemrini and Carreras.³⁻⁵ The exploration was systematically begun on the right eye, and later continued on the left eye.

The subject was instructed to look directly into the light source, and the dazzle was produced by the flash apparatus located 1.5–2 cm from the cornea. At the instant at which the dazzle was produced the chronometer was set in motion, and from this moment on the recording of the recovery time began, with the chronometer stopping at the moment when the subject reached the same visual acuity (same line on the optotype) as before the dazzling. The test was repeated for short distance vision, the short distance optotypes being used as a point of reference.

We have studied the influence of the dilatation of the pupil and of miosis in relation to the test results in 65 subjects of the sample. For this purpose two drops of phenylephrine chlorhydrate were put into the right

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eyes of these 65 subjects, and two drops of 2% pilocarpine were put into their left eyes. They underwent the same procedure described above, when the right pupils reached a diameter of 7–8 mm and the left a diameter of 2–3 mm.

Results

The MDT recovery time was statistically ($p < 0.001$) longer for long distance vision ($\bar{x} = 15.49$ s) than for short distance vision ($\bar{x} = 11.61$ s) (Table 1). The range of variation observed for long distance vision was found to be 7 seconds (a total of 5 cases—2.1%—between the second and third decades of their lives) and 35 seconds (3 cases—1.25%—distributed among the first, fifth, and sixth decades). A similar range was also observed for short distance vision: 5 seconds for the minimum value (two cases in the second and third decades—0.8%) and 50 seconds for the maximum value in one case—0.4%—in the fifth decade.

Table 1 MDT results on a normal population

No people studied: 120, (240 eyes)
Sex distribution: 1.1 males females
Age distribution: 6 groups of 20 patients each from 10–69 years of age.
Total mean duration:
MDT long distance vision
n = 240 eyes
$\bar{x} = 15.49 \pm 5.76$ s
MDT short distance vision
n = 240 eyes
$\bar{x} = 11.61 \pm 6.30$ s
Significance of differences $p < 0.001$
Range:
MDT long distance vision: 7–35 s
MDT short distance vision: 5–50 s

Table 2 MDT results related to eye laterality (right or left eye)

MDT long distance vision:	
RE:	n = 120 eyes
	$\bar{x} = 15.89 \pm 6.22$ s
	range: 7–35 s
LE:	n = 120 eyes
	$\bar{x} = 15.10 \pm 5.24$ s
	range: 7–35 s
Significance of differences $p > 0.1$	
MDT in short distance vision:	
RE:	n = 120 eyes
	$\bar{x} = 11.48 \pm 6.09$ s
	range: 5–45 s
LE:	n = 120 eyes
	$\bar{x} = 11.73 \pm 6.54$ s
	range: 6–50 s
Significance of differences: $p > 0.1$	
Significance of differences between MDT (Long) and MDT (short):	
RE:	$p < 0.001$
LE:	$p < 0.001$

The values obtained from the MDT were similar in the right and left eyes of the subjects, both for long distance vision and for short distance vision. Nevertheless some differences were apparent when a comparison is made between the figures for long distance vision and short distance vision, with those for short distance vision being significantly lower (Table 2).

Differences in MDT values between the sexes were not observed; the figures for both male and female subjects were similar for long distance vision, though there was a slight difference in their short distance vision (Table 3).

The recovery time for the MDT showed a clear tendency towards increase with aging, both for long distance vision and short distance vision, the means being accompanied by a general increase of standard deviations (Table 4). We have also demonstrated the existence of a high correlation between the means and the standard deviations of the different age groups (Figs. 1A and 1B). This increase in the MDT with an increase in age became clearer when a comparison was made between the values for the

Table 3 MDT results related to sex difference

MDT long distance vision	
Males:	Females:
n = 120 eyes	n = 120 eyes
$\bar{x} = 15.03 \pm 5.40$ s	$\bar{x} = 15.95 \pm 6.08$ s
range: 7–35 s	range: 8–35 s
Significance of differences: $p > 0.1$	
MDT short distance vision:	
Males:	Females:
n = 120 eyes	n = 120 eyes
$\bar{x} = 10.83 \pm 4.99$ s	$\bar{x} = 12.38 \pm 7.33$ s
range: 5–50 s	range: 5–45 s
Significance of differences: $p < 0.01$	

Table 4 MDT duration in age groups

MDT long distance vision (seconds)		
Age group	$\bar{x} \pm SD$	Range
10–19	13.88 $\pm$ 5.19	8–35
20–29	12.78 $\pm$ 3.81	7–21
30–39	13.47 $\pm$ 3.41	7–20
40–49	15.25 $\pm$ 4.96	8–26
50–59	18.13 $\pm$ 7.14	8–35
60–69	19.44 $\pm$ 6.07	11–35
MDT short distance vision (seconds)		
Age group	$\bar{x} \pm SD$	Range
10–19	8.93 $\pm$ 1.70	6.5–12
20–29	8.50 $\pm$ 2.53	5–15
30–39	9.05 $\pm$ 1.80	5–13
40–49	12.25 $\pm$ 4.10	7–21
50–59	14.13 $\pm$ 9.22	7–50
60–69	16.80 $\pm$ 8.41	8–45

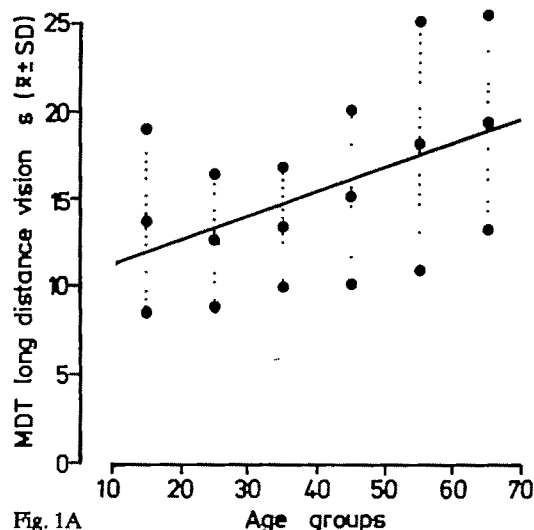


Fig. 1A

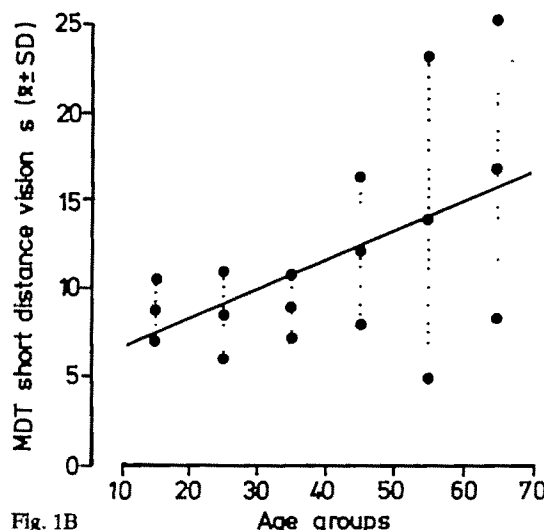


Fig. 1B

Fig. 1A Analysis of the distribution of means and standard deviations related to recovery time of the MDT for long distance vision, in the different age groups, by the linear correlation method. $r=0.902$; $\bar{x}=-75.46$; $y=9.81$.

Fig. 1B Analysis of the distribution of the means and standard deviations related to recovery time of the MDT for short distance vision, in the different age groups, by the linear correlation method. $r=0.94$; $\bar{x}=-31.3$; $y=5.01$.

subjects under 40 years of age and those aged 40 and over (Table 5).

Figs. 2A and 2B show a better distribution of the percentage of eyes towards the lowest values.

The MDT was not influenced by the diameter of the pupil when the pupil is mydriatic and when the test is being made on long distance vision; however, the recovery time for short distance vision is longer. The MDT values with a miotic pupil showed a significant reduction in the recovery time, both for long distance vision and short distance vision, when these values were compared with those of a normal pupil and without the application of any type of pharmaceutical product to the eyes (Table 6).

Discussion

The MDT is an easy test to perform. It can be done

quickly (under 3 minutes) and its results can be repeated with a minimum of collaboration from the patient.

Most authors^{1,2,4,8} have used the light of their ophthalmoscope to produce the dazzling, varying the light exposure from 15 seconds to 1 minute.⁸ Although some of them^{1,2,7} place no importance on, or at least do not report, the intensity of the light, others vary the light's intensity. Forsius⁴ used 2145 lux, previously adapting the patient to the darkness for a one-hour period; and Tiburtius⁸ used an intensity of 50 lux. Glaser⁹ used a light source consisting of a light bulb which produced 2340 lux instead of an ophthalmoscope. We used a conventional electronic flash, like Lemrini and Carreras,³ as this technique is faster and it readily produces a true dazzling of the macula; in addition there is no need for exceptional collaboration by the subject being examined. In contrast, both the light bulb used by Glaser⁹, and especially an ophthalmoscope light,

Table 5 MDT results related to age: under 40 years and 40 years and over

MDT long distance vision:	
Age under 40 years	n=120 eyes $\bar{x}=13.88 \pm 4.20$ s
Age 40 years and over	n=120 eyes $\bar{x}=17.61 \pm 6.32$ s
Significance of differences	$p<0.001$
MDT short distance vision:	
Age under 40 years	n=120 eyes $\bar{x}=8.83 \pm 2.21$ s
Age 40 years and over	n=120 eyes $\bar{x}=9.96 \pm 6.13$ s
Significance of differences	$p<0.001$

Table 6 MDT results related to the pupil diameter

MDT mydriasis (RE).	MDT miotics (LE)
long distance vision:	long distance vision
n=65 eyes	n=65 eyes
$\bar{x}=15.83 \pm 9.78$ s	$\bar{x}=12.75 \pm 7.37$ s
range: 6-70 s	range: 5-63 s
short distance vision:	short distance vision.
n=65 eyes	n=65 eyes
$\bar{x}=14.20 \pm 19.83$ s	$\bar{x}=9.96 \pm 6.13$ s
range: 4.5-115 s	range: 4-36 s

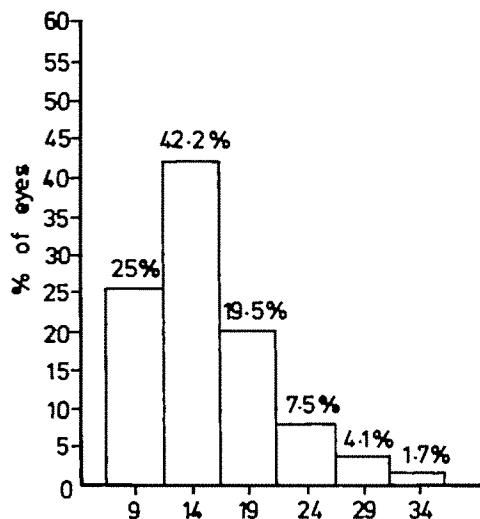


Fig. 2A MDT long distance vision (s)

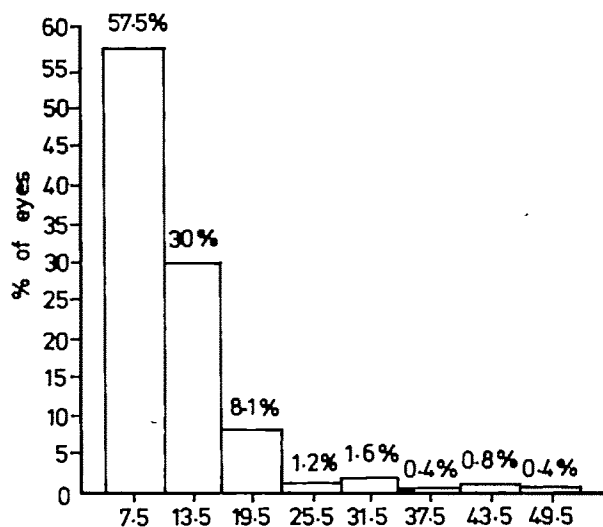


Fig. 2B MDT short distance vision (s)

Fig. 2A Histogram of frequencies of recovery time of the MDT for long distance vision, on 240 healthy eyes, with a mean of 15.49 s and SD 5.76 s.

Fig. 2B Histogram of frequencies of recovery time of the MDT for short distance vision, on 240 healthy eyes, with a mean of 11.61 s and SD 6.30 s.

require a greater amount of patient collaboration, because he must concentrate his attention on the light source constantly for a period which varies from 10 to 60 seconds. Moreover the dazzling is possibly less. On the other hand the use of the conventional electronic flash, proposed by Lemrini and Carreras,³ avoids the sophisticated instruments like those used by Severin and his collaborators⁸ which, although they are more precise, do not invalidate our results, in addition to their being more difficult to use under the conditions of routine clinical examinations.

The instruments used by Severin and his collaborators⁸ consist of a Meyer-Swickerath Zeiss light coagulator, a Goldmann-Weekers adaptometer, and a shutter, require in addition a -10 dioptré lens to diverge the beam of light and to light up the entire retina. This is not entirely necessary because the MDT really explores the macular visual acuity, and the lighting of the macula can be done perfectly well with a flash on which the patient focuses his eyes directly, thus making the use of a diverging lens unnecessary.

The mean value of the MDT for long distance vision (15.49 s) falls within the figures considered normal in published reports,¹⁻¹² with ours being the second lowest after those of Lemrini and his collaborators.³⁻⁵ This means that the reactions are more or less comparable and that they fall within similar values, with the values obtained depending on the type of light source used and on the method

followed. In addition the age of the population on which the study is made must be taken into account, as we have shown that the recovery time following the dazzling is longer as the age of the subject increases, which has been pointed out by other authors,^{3-5, 8, 10-12} though Glaser⁶ did not find that the MDT increases significantly with age. It must be pointed out that the standard deviations increase simultaneously with the increase in the mean recovery time of the MDT with age. This increase in the mean value of the MDT with age is one more indicator of the involutional senile phenomenon, to which eyes are no exception. We must not forget the modifications which are produced with aging on the Bruch membrane complex and pigmentary epithelium.¹³⁻¹⁶ Neither the sex of the subject nor the eye studied (the right eye or the left eye) has any influence on the results of the MDT though Forsius⁴ found that in females the values are higher in the 10 to 39-year-old group.

From what we have previously stated, and taking into account that the test is independent of other different age parameters, we consider, as the *criterion of normality*, that in eyes to which no pharmaceutical product has been applied those values which fall between the mean and a standard deviation (69% probability) are *probably normal*, and that those which fall between the mean and two standard deviations (95% probability) in each age group are *truly normal*. However, in absolute terms

values greater than 32 seconds could be considered pathological. Or, if we compare the difference of the MDT in each eye of the same subject, for a probability index of 95% it is possible to accept differences between the right and left eye of up to 15.61 seconds for the first three decades and 22.15 seconds for the fourth, fifth, and sixth decades of life.

The dilatation of the pupil from 7 to 8 mm does not significantly modify the results of the MDT but miosis does. Miosis reduces the recovery time $\bar{x} = 12.75$ s, though it does not reach the figures given by Severin and his collaborators,¹⁰ who refers to a reduction of up to 50%. This would be a factor to consider with patients on miotics. The difference between mydriasis and miosis is difficult to explain, though the influential factors are the smaller amount of light that passes through a closed pupil, with a less dazzling effect, and the action itself of the stenopaic hole which miosis of the pupil brings about.

The MDT performed for short distance vision, like that for long distance vision, shows no significant differences in the results in relation to which eye is explored, right or left, or the sex of the subject. It also increases progressively with age. There are significant differences between the subjects under 40 and those aged 40 and over. In addition the recovery times are reduced with miosis of the pupil.

If all the results obtained for short distance vision are compared with those for long distance vision, it can be observed that in all of the parameters analysed the reactions of the MDT are significantly reduced, which indicates a variability in the test according to whether the analysis is made at a short or at a long distance. These discrepancies, which are repeated in the different subjects analysed, could be due in part to the larger size of the retinal image in short distance vision—thus a greater clarity—and the reduction of the diameter of the pupil which is brought about on looking at something at a short distance (we have previously commented on how the MDT is reduced at a long distance with miosis), and to other factors such as the angular value of the optotype for short distance vision, brightness, etc.

There are no reports analysing the MDT for short distance vision, but since the results are homogeneous and this is a macular exploration test, its study in relation to short distance vision would seem

logical, given the fact that there are existing differences in relation to long distance-short distance vision, which the MDT can clarify.

Although the purpose of this work is not the study of the MDT in macular pathology (this will form part of a second publication), we have observed cases of central serous retinopathy in which the MDT is pathologically prolonged, both for long distance vision and short distance vision. However, as regards short distance vision, the recovery time is double that of long distance vision when, as we have already seen, under physiological conditions the normal situation is the reduction of the recovery time for short distance vision.

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Effects on perceptual development of visual deprivation during infancy

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SUMMARY We measured three aspects of vision in children treated for unilateral congenital cataract: visual resolution, the symmetry of optokinetic nystagmus (OKN), and peripheral vision. Good visual resolution was achieved by children who had had the earliest treatment and who had had the normal eye patched close to 50% of the waking time throughout early childhood. All children treated for unilateral congenital cataract showed a marked asymmetry of OKN regardless of the age of treatment. One child with early treatment who could be tested with the Goldmann perimeter also showed especially poor sensitivity in the nasal visual field of her aphakic eye. We found no such deficits in the vision of children who had had normal visual experience during early infancy and then later developed cataracts in one or both eyes. The limitations observed in children treated for congenital cataract are similar to those reported in normal human infants, in normal kittens, and in cats which were visually deprived early in life.

Much of what we know about the effects of visual deprivation comes from studies of cats which had one eye sutured shut during a critical period shortly after birth. Such cats later show limitations in many aspects of vision, including visual resolution,¹ peripheral vision (reviewed by Maurer and Lewis²), and the symmetry of optokinetic nystagmus.^{3,4} These three aspects of vision are also poorly developed in normal kittens^{5,6} and in normal human infants.⁷⁻¹¹

We were interested in determining whether monocular deprivation during early infancy affects the development of these abilities in humans as it does in cats. To do so we turned to a population of children who had been born with a dense, central cataract in one eye. (This condition is similar to lid suture in cats because only diffuse light passes through the cataract.) The cataract had been treated surgically by removing the natural lens of the eye, rendering the eye aphakic. The aphakic eye was fitted with a contact lens which restored nearly normal visual input. Parents were then instructed to patch the normal eye 50% of the waking time. We measured three aspects of vision in these children: visual resolution, the symmetry of optokinetic nystagmus (OKN), and peripheral vision.

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Experiment I. Visual Resolution

Visual resolution has been tested both in normal kittens and in normal human infants by showing subjects black-and-white stripes of varying width paired with a grey stimulus of the same mean luminance. The width of the smallest stripes chosen over grey provides a measure of visual resolution. Numerous studies have shown that visual resolution is poorly developed at birth both in cats¹ and in humans.¹²

Adult cats which had been monocularly deprived for a period after birth also show poor visual resolution in the previously deprived eye. The best visual resolution achieved depends on the *duration* of deprivation such that, the longer the deprivation, the poorer the visual resolution.¹ However, the visual resolution of the formerly deprived eye can be improved if the normal eye is sewn shut when the deprived eye is opened,¹ a procedure called *reverse-suturing*. The visual resolution of visually deprived cats also depends on the *timing* of deprivation. Giffin and Mitchell¹³ demonstrated this in cats which were monocularly deprived for 23 days beginning at 42, 64, or 87 days of age. Only the cats which had been monocularly deprived from 42 days of age failed to recover normal visual resolution in the deprived eye. Thus in cats the effect of deprivation on the develop-

ment of visual resolution depends on when the deprivation begins, how long it lasts, and whether or not reverse-suturing occurs. The purpose of the first experiment was to determine whether similar principles apply to humans who had been monocularly deprived.

MATERIALS AND METHODS

We measured the Snellen acuity of 13 children who had been deprived from birth for varying periods of time because of a dense and central congenital cataract in one eye (congenital group). For comparison we measured the Snellen acuity of 30 children who had had normal visual experience until an injury caused a dense central cataract to develop in one eye sometime after the age of 3 years (traumatic group). During the Snellen test the aphakic eyes were corrected optically to focus at infinity.

RESULTS AND DISCUSSION

Fig. 1 shows the Snellen acuity of the deprived eye for the congenital group plotted as a function of duration of deprivation, that is, the time from birth until the cataract was removed surgically and the aphakic eye fitted with an appropriate contact lens. The two

children who had had the shortest periods of deprivation and who had had the normal eye patched close to 50% of the waking time throughout early childhood had the best Snellen acuities (6/12 and 6/15). The remaining 11 children who had poorer Snellen acuities had had longer periods of deprivation and/or little or no patching of the normal eye.

Fig. 2 shows the Snellen acuity of the deprived eye for the traumatic group plotted as a function of duration of deprivation, that is, the time from when the cataract was first diagnosed as dense and central until the cataract was removed surgically and the aphakic eye fitted with an appropriate contact lens. All but five children had Snellen acuities of at least 6/18, regardless of the duration of deprivation and regardless of whether or not they had patched the normal eye. The five children with Snellen acuities worse than 6/18 had all had long periods of deprivation (more than one year) beginning before 6 years of age.

Table 1 summarises the results and shows that the median acuity is influenced both by the duration and by the timing of deprivation. A comparison of the columns in Table 1 shows that Snellen acuity tended to be better in children who had had relatively short periods of deprivation (less than six months) than in children who had had longer periods of deprivation. A comparison of the rows in Table 1 shows that Snellen acuity tended to be better in children deprived after 3 years of age than in those deprived

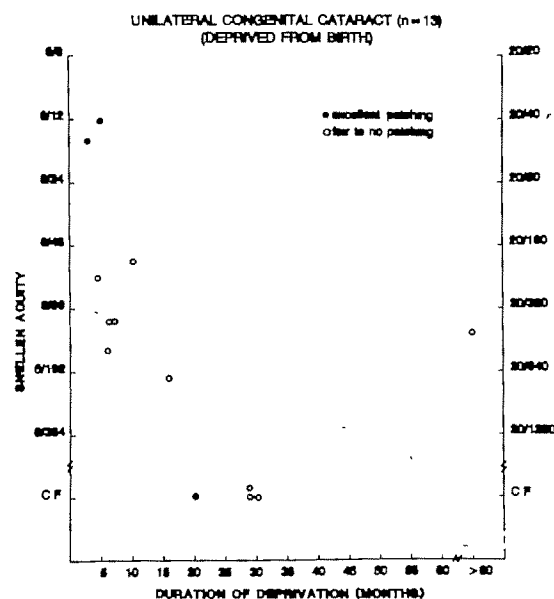


Fig. 1 Snellen acuity as a function of duration of deprivation in the aphakic eye of children treated for unilateral congenital cataract. Snellen acuities are shown in metres on the left axis and in feet on the right axis. Filled circles represent the results from children who had had the normal eye patched close to 50% of the waking time throughout early childhood. Open circles represent the results from children who did not.

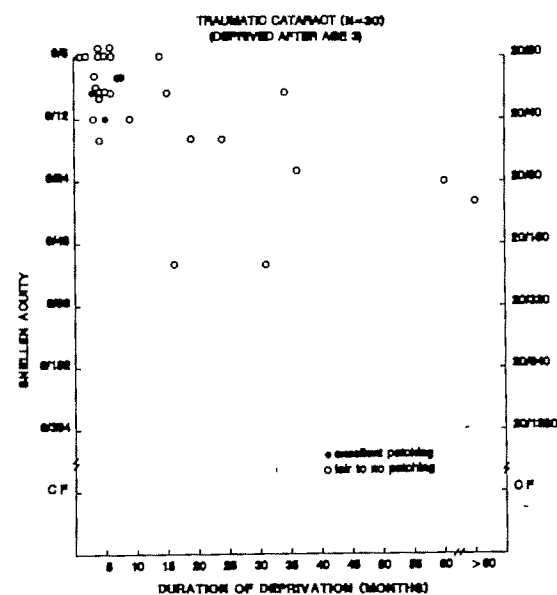


Fig. 2 Snellen acuity as a function of duration of deprivation in the aphakic eye of children treated for traumatic cataract. Other details as in Fig. 1.

Table 1 Median acuity as a function of duration and timing of deprivation

	Duration of deprivation	
	<6 months	≥6 months
Deprivation beginning from birth (congenital cataract)	6/15	6/190
Deprivation later (traumatic cataract)		
Beginning age 3 to 6	6/10.5	6/24
Beginning after age 6	6/7.5	6/8

from birth. Moreover, there appears to be an interaction between duration and timing of deprivation such that the worst acuities were shown by children who had had long periods of deprivation beginning at birth. What is not illustrated in Table 1 is that the potentially poor outcome of early deprivation can be tempered by regular patching of the normal eye.

In summary, our results from tests of Snellen acuity show that visual deprivation during infancy does not prevent the development of good visual resolution, provided the deprivation is short and provided that, following the deprivation, the normal eye is patched regularly. Deprivation at a later age does not lead to the same deficiencies. These results are similar to those from monocularly deprived cats.¹⁵

Experiment II. Symmetry of optokinetic nystagmus

A second aspect of vision measured in monocularly deprived children was the symmetry of optokinetic nystagmus. OKN is a series of jerky eye movements elicited by a repetitive pattern moving across the visual field. Thus the eyes follow a part of the pattern (slow phase) and then saccade back to pick up another part (fast phase). In normal adult humans and cats OKN can be elicited easily both when stripes move from the temporal visual field toward the nasal field (for example, from right to left for the right eye) and when they move from the nasal visual field towards the temporal visual field (for example, from left to right for the right eye).^{12,13} Thus their OKN is 'symmetrical'. In contrast, young human infants and kittens show consistent OKN when stripes move temporally to nasally but little or no OKN when stripes move in the opposite direction.^{14,16} We refer to this difference in the ease of eliciting OKN in the two directions as 'asymmetrical OKN'.

Like human newborn babies and kittens, cats which were monocularly deprived shortly after birth also show asymmetrical OKN.^{14,17} Moreover, this asymmetry is present both in the previously deprived eye and in the non-deprived eye^{14,17} (but see Malach

*et al.*⁶). To determine whether deprivation affects similarly the symmetry of OKN in humans monocularly deprived from birth, we tested children treated for a dense unilateral congenital cataract (congenital group). For comparison, we also tested normal subjects and children who had had normal visual experience until they incurred a traumatic cataract sometime after 3 years of age (traumatic group).

MATERIALS AND METHODS

The congenital group consisted of 17 children who had had a dense central cataract diagnosed in one eye at a median age of 2 months (range birth to 6 months). The cataract had been removed surgically at a median age of 5.5 months (range 2 to 28 months) and the aphakic eye fitted with an appropriate contact lens at a median age of 9 months (range 3 to 29 months). At the time of the asymmetry test the children ranged in age from 1 to 13 years (median = 5 years). Refractive errors ranged from +2.0 D to +24.75 D (median = +16.5) in the aphakic eyes and from plano to +3.0 D (median = plano) in the normal eyes. For the eight children old enough to read an eye chart Snellen acuities ranged from 6/12 to merely light perception (median = 6/60) in the aphakic eyes and from 6/6 to 6/7.5 (median = 6/6) in the normal eyes. We tested the normal eye of all 17 children but were able to test only six aphakic eyes primarily because of latent nystagmus in many cases.

The traumatic group consisted of 13 children who had incurred a dense cataract at a median age of 8.5 years (range 3 to 13 years). The cataracts had been removed surgically at a median age of 9 years (range 3 to 13 years), and the aphakic eyes had been fitted with an appropriate contact lens at a median age of 9 years (range 3 to 14 years). The median duration of deprivation was five months (range 1 to 34 months). At the time of the asymmetry test the median age of this group was 12 years (range 3 to 17 years). Their refractive errors ranged from +10.5 D to +17.5 D (median = +14.0 D) in the aphakic eye and from plano to -1.0 D (median = plano) in the normal eye. The 12 children old enough to read an eye chart had Snellen acuities ranging from 6/6 to 6/30 (median = 6/12) in the aphakic eye and from 6/6 to 6/9 (median = 6/6) in the normal eye. We tested the aphakic eye of all 13 children and the normal eye of eight.

The normal subjects ($n=26$) ranged in age from 1 year to adulthood (median age = 4 years). We tested the right eye of half the subjects and the left eye of the other half.

For the OKN test each subject had one eye occluded and sat 50 cm from a 90° × 90° rear projection screen surrounded by black plywood. Black-

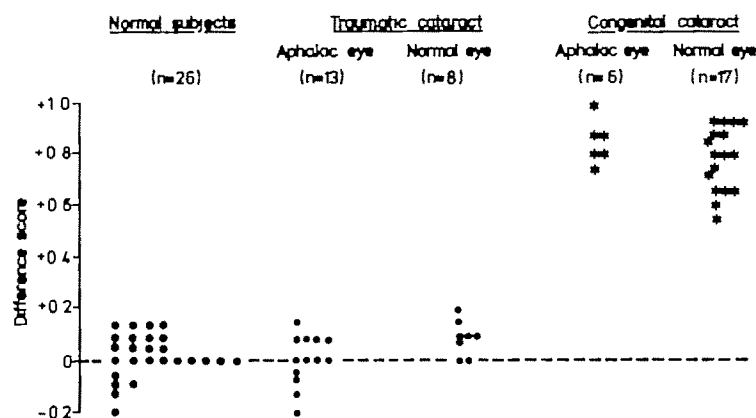


Fig. 3 Asymmetry of OKN in three groups of subjects. See text for details.

and-white vertical stripes (0.6 cycles/deg) were swept across the screen at a velocity of 13 deg/s by a 35 mm slide projector projecting through a rotating mirror. Shielded peepholes on either side of the screen permitted a clear view of the subject's unoccluded eye, but not of the stimuli. The test included 39 randomly ordered 7 s trials: 15 trials with stripes moving temporally to nasally, 15 trials with stripes moving nasally to temporally, and 9 control trials with a moving blank field. An observer decided during each trial whether OKN definitely occurred, possibly occurred, or definitely did not occur.

RESULTS AND DISCUSSION

The observer never reported definite OKN when the field was blank except during one trial for one subject.

For each eye, we used a two-tailed χ^2 test to compare the frequency of trials on which OKN definitely occurred when stripes moved temporally to nasally versus the frequency when stripes moved nasally to temporally. Fig. 3 shows the difference between these two frequencies for each eye tested. A positive difference score means that definite OKN was observed on a greater proportion of trials when stripes moved temporally to nasally than when they moved nasally to temporally. Conversely, a negative difference score means that OKN was observed on a greater proportion of trials when stripes moved nasally to temporally than when they moved temporally to nasally. An asterisk indicates that a difference was significant by the χ^2 test (that is, asymmetrical OKN) and a dot indicates that a difference was not significant (that is, symmetrical OKN).

In normal subjects and in both eyes of children treated for traumatic cataract definite OKN was observed on virtually every experimental trial. Thus their difference scores tended to cluster around zero, and in no case was there a significant asymmetry by the χ^2 test (see Fig. 3). In contrast for the congenital

group definite OKN was observed on most trials when stripes moved temporally to nasally but on few trials when stripes moved nasally to temporally. Thus in this group all the difference scores were positive and the asymmetry was significant by the χ^2 test in every aphakic and normal eye tested. The magnitude of the asymmetry was not related to the duration of deprivation nor to the patching regimen. Children who had had early treatment and aggressive patching of the normal eye had asymmetries just as large as those who had had later treatment with little or no patching of the normal eye.

Factors other than early pattern deprivation *per se* might have contributed to the observed asymmetries. For example, asymmetrical OKN has been reported in subjects with amblyopia,^{13,14} with esotropia,^{15,16} or with reduced stereopsis for whatever reason.¹³ However, none of these factors was more common in children in the congenital group, all of whom showed asymmetrical OKN, than in children in the traumatic group, none of whom showed asymmetrical OKN.

Like our findings for visual resolution the timing of deprivation appears to affect the development of symmetrical OKN. Children deprived from birth showed a marked asymmetry of OKN, but those deprived after 3 years of age showed no such marked asymmetry. However, unlike visual resolution the symmetry of OKN appears to be unaffected by the duration of deprivation, at least when deprivation lasts between three and 29 months after birth or between one and 34 months after age 3. Even short periods of deprivation early in life, which affect minimally the development of visual resolution, abolish the symmetry of OKN. Thus, as in animals,¹ deprivation affects different visual functions during different critical periods.

Experiment III. Peripheral vision

Throughout the first six weeks of life kittens are less

likely to orient towards objects in the nasal visual field (for example, the left visual field when looking with the right eye) than towards objects in the temporal visual field (for example, the right visual field when looking with the right eye).⁷ Recently we reported a similar pattern of results in young human infants shown lines of varying width located either at 30° in the temporal visual field or at 20° in the nasal visual field.¹¹ We assumed that, if infants could see a line, they would look towards it more often than they looked in the same direction on control trials when the field was blank. When lines were located at 30° in the temporal visual field 1-month-old infants detected the narrowest line we presented, a line only 1.5° wide. In contrast, when lines were located at 20° in the nasal visual field, they detected a 'line' 25.6° wide but showed no evidence of detecting a line even 12.8° wide. Thus 1-month-olds show at least an eightfold difference in the size of line they can detect at those locations. Normal adults on the other hand are *better* at detecting objects located at 20° in the nasal visual field than objects located at 30° in the temporal visual field.¹⁴

Cats which were monocularly deprived during a critical period shortly after birth, like young human infants and kittens, are especially poor at detecting stimuli in the nasal visual field of the deprived eye⁷ reviewed by Maurer and Lewis.² To determine whether monocular deprivation has similar effects in humans we used the Goldmann perimeter to measure sensitivity along the horizontal meridian in one child treated for a unilateral congenital cataract. For comparison we also tested a child with no known eye disorders and children who had normal visual experience until they developed cataracts in one or both eyes.

MATERIALS AND METHODS

Two subjects, A and B, were tested extensively. Patient A was a 12-year-old child who had had a dense central cataract diagnosed in her left eye by 3 months of age. The cataract was removed at 4½ months and the aphakic eye fitted with a contact lens at 5 months. Subsequently her normal eye had been patched at least 50% of the waking time throughout early childhood, and at the time of the perimetry test she had 6/12 acuity in her aphakic eye and 6/6 acuity in her normal eye. Patient B was a 13-year-old child with 6/6 vision in each eye and no known eye problems. Five additional eyes from four children were tested less extensively by perimetry. All of these children had had normal visual experience and then developed dense, central cataracts in one eye or both eyes. Three of these patients had had developmental cataracts and one a traumatic cataract. Other details are listed in Table 3.

We used the Goldmann perimeter to test each eye of patient A with a 6.25 min spot of light (object I) and with a 13 min spot of light (object II) every 10° along the horizontal meridian from 30 to 60° in the temporal visual field, and from 10 to 60° in the nasal visual field. For comparison we tested one eye of patient B with a 6.25 min spot of light at the same locations. The remaining subjects were tested only at 30° in the temporal visual field and at 20° in the nasal visual field. In each case the subject's task was to identify the one of two 2 s intervals during which a spot of light had appeared. At each location we used a staircase to determine the intensity at which the subject could identify the correct interval 75% of the time (PEST with $W=1$, initial step size = 1 log ml; final step size = 0.05 log ml).¹⁵

RESULTS AND DISCUSSION

The results for patients A and B are shown in Figs 4 (6.25 min spot) and 5 (13 min spot). At every location A required more intensity to detect light with her aphakic eye than with her normal eye, which gave results similar to those from the normal control

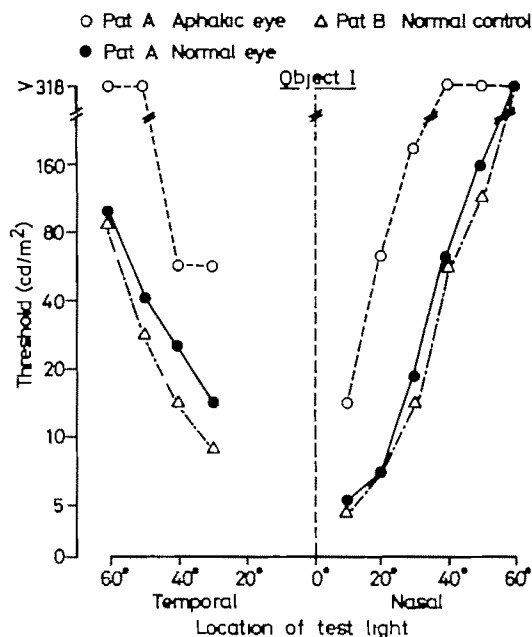


Fig. 4 The threshold luminance for detecting a 6.25 min spot of light (object I) at various locations along the horizontal meridian for the aphakic and normal eyes of patient A, who was treated for a unilateral congenital cataract, and for one eye of patient B, who had no known eye disorders. We did not test 20° in the temporal visual field because the blind spot interferes with the detection of small targets at that location.

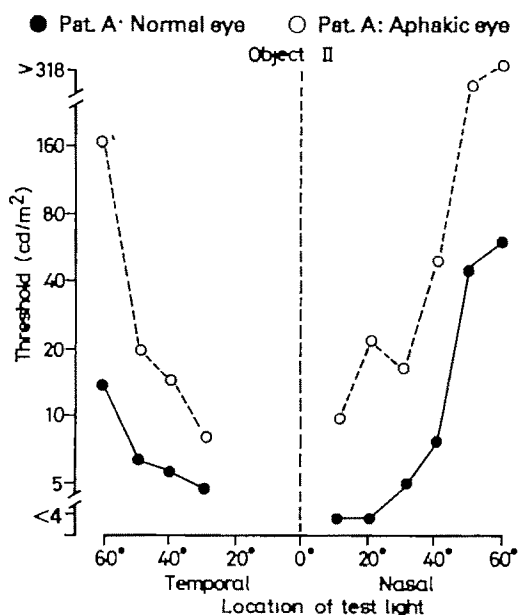


Fig. 5 The threshold luminance for detecting a 13 min spot of light (object II) at various locations along the horizontal meridian for the aphakic and normal eyes of patient A. Other details as in Fig. 4.

Table 2 Threshold intensities for patient A (treated for unilateral congenital cataract) and B (normal control subject) at 20° in the nasal visual field and at 30° in the temporal visual field

Subject	Condition	Object size	Threshold (cd/m ²)	
			20° Nasal	30° Temporal
A	Aphakic eye	I	63.5	56.6
		II	22.5	8.5
A	Normal eye	I	7.1	14.2
		II	<4.0	4.8
B	Normal	I	7.1	9.0
		II	<4.0	4.5

subject, B. Table 2 summarises the threshold intensities for patients A and B at 20° in the nasal visual field and at 30° in the temporal visual field, the locations we had tested in normal 1-month-olds.¹¹ Like patient B and like normal adults,¹² A's normal eye had lower thresholds at 20° in the nasal visual field than at 30° in the temporal visual field. In contrast, unlike normal adults but like normal 1-month-olds, A's aphakic eye had *higher* thresholds at 20° in the nasal visual field than at 30° in the temporal visual field.

Table 3 lists thresholds for lights at those locations in the children who had had normal visual experience until they later developed cataracts. In every case threshold intensity at 20° in the nasal field was equal to, or lower than, threshold intensity at 30° in the temporal field. This pattern is like that of normal adults and very different from the pattern we observed in the aphakic eye of patient A, the child treated for a unilateral congenital cataract. It is evident that aphakia per se does not account for greater threshold elevation (that is, lower sensitivity) in the nasal as compared with the temporal field.

It is also unlikely that associated problems such as amblyopia or strabismus accounted for the results. Patient A had achieved 6/12 vision in her aphakic eye and showed especially poor detection in the nasal visual field, while one child in the control group (patient E) who had only 6/120 vision in her aphakic eye showed no such nasal field loss. Patient A also had only a slight, variable tropia (4° esotropia to 6° exotropia at near; 6° to 8° of exotropia at far), and the literature suggests no consistent effect of strabismus on peripheral vision.^{20,21} It seems likely that our finding of especially poor detection in the nasal visual field of A's deprived eye is related at least in part to the visual deprivation caused by a congenital cataract. If that is the case, then early visual deprivation affects the development of humans' visual fields in much the same way it affects the

Table 3 Threshold intensities for subjects who developed cataracts after birth

Subject	Condition	Age of diagnosis (months)	Duration of deprivation (months)	Age at test (years)	Snellen acuity	Object size	Threshold (cd/m ²)	
							20° Nasal	30° Temporal
C	Dev OD ¹	12	5	8.5	6/15	I	28.4	56.6
	Dev OS	7.5	6.5	8.5	6/12	I	14.2	112.9
D	Dev OD	17	6	7.5	6/9	III	4.5	89.7
	Dev OS	Not tested because of secondary membrane						
E	Normal OD	Not tested						
	Dev OS	20	4	10	6/120	II	28.4	35.7
F	Traum OD ²	145	5	13	6/7.5	II	5.7	5.7
	Normal OS	—	—	13	6/6	II	<4.0	4.5

¹Developmental cataract.

²Traumatic cataract.

development of kittens' visual fields. In both cats and humans deprivation depresses sensitivity in the nasal visual field, so that, like the young human infant or the young kitten, the deprived eye is less sensitive to stimuli in the nasal field than at corresponding locations in the temporal field.

Conclusions

We have discussed three aspects of vision which are incompletely developed at birth in cats and in humans: visual resolution, the symmetry of OKN, and peripheral vision. In cats these abilities are adversely affected by monocular deprivation early in life. Thus after such deprivation visual resolution is reduced, OKN is asymmetrical, and cats fail to orient toward objects in the nasal visual field. After short periods of deprivation, some of these effects are reversible, especially if the normal eye is then sutured shut. Deprivation at a later age does not lead to the same deficiencies. Our results so far suggest that these same principles apply in humans who have been visually deprived in one eye during early infancy by the presence of a dense central cataract.

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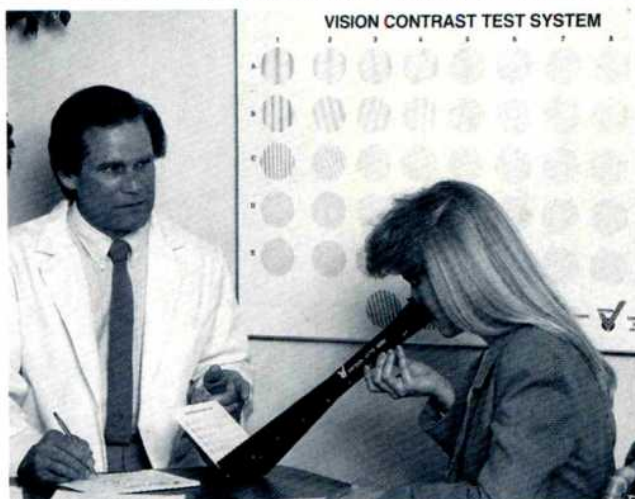
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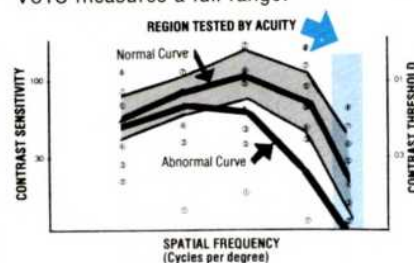
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Critical evaluation of the NR-1000F Auto Refractometer

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SUMMARY The manifest (dry) refractions of 165 eyes of 86 patients, aged 6 to 75 years, were studied on the Nikon Auto Refractometer NR-1000F. The results obtained were compared with the clinical refractive data, and they were analysed for degree of agreement of various refractive components in different types and grades of refractive errors in the separate age groups. On the NR-1000F the spherical and cylindrical components and spherical equivalents skewed towards more minus (or less plus), especially so in emmetropes, low hypermetropes, and low myopes. This error declined with increasing age over 40 years and was also significantly lower in aphakia and mixed astigmatism. Determination of cylinder axis was found to be reliable on the NR-1000F. In spite of the obvious utility of the device its inbuilt automatic fogging system does not seem adequately to neutralise the patient's accommodative efforts, as the fixation target probably induces instrument myopia.

Automatic refractors have gained importance in recent years because of the busy clinical schedule of ophthalmologists and the increasing faith of patients in sophisticated mechanical devices. Many such refractometers, both subjective and objective, are now available, with steadily improving designs and claims to accuracy.¹ One of the latest objective models is the Nikon Auto Refractometer NR-1000F, which was recently installed in our centre. In view of several reports in the literature on the reliability and accuracy of various types of autorefractors²⁻⁴ we considered it worthwhile to undertake a systematic study to evaluate the NR-1000F Auto Refractometer (AR) before putting this instrument into routine general use in our busy hospital schedule.

Materials and methods

In the NR-1000F Auto Refractometer infrared rays are directed at the patient's fundus and the reflected light is detected by this instrument. A built-in microcomputer deduces the objective refraction in terms of sphere, cylinder, and axis, and then automatically displays this information, corrected for a 12 mm vertex distance. The AR also has the optional facility of automatic printout of the refractive data obtained, and is capable of recording a confidence

value for each result to quantify numerically the reliability of the measurement. It completes each objective measurement in a total of 1.5 seconds, with the final measurement in only 0.5 seconds. The time taken for automatic fogging is 0.5 to 1 second with the patient seeing the fixation target, while the patient's accommodation is purportedly thoroughly relaxed by the inbuilt automatic fogging system. The machine can measure up to ± 15 D sphere and ± 6 D cylinder.

In accordance with the instructions in the operating manual supplied by the manufacturers the NR-1000F is placed in a dimly lit, cool, and dust-free room. After a latent period of about 10 seconds on turning on the power switch a musical sound indicates that the machine is ready for use. The operator then manipulates the dioptre adjusting ring till the cross reticule at the centre of the viewfinder appears sharply in focus. The patient is seated comfortably, and the eye to be refracted is aligned to the correct level with the measuring head. A small child finds it easier to stand at the instrument. A model eye supplied may be used for operator practice as well as for an instrument check.

The green cross targets are aligned and centred by the operator with the peripheral red arrows moved out of the field of view to ensure precise positioning of the measuring head. The start button is depressed to activate the in-built automatic fogging system, and the refractive data are available within 1.5 seconds on

Table 1 Refractive error and distribution by age of 86 patients (165 eyes)

Age group (years)	No of patients	Type of refractive error (no of eyes)					Total no of eyes
		Emmetropia	Myopia	Hypermetropia	Aphakia	Mixed astigmatism	
<10	3	1	2	3	0	0	6
11-20	31	10	34	15	0	1	60
21-30	26	15	26	10	0	0	51
31-40	10	4	4	12	0	0	20
41-50	5	0	10	0	0	0	10
>50	11	0	3	7	6	2	18
Total	86	30	79	47	6	3	165

the digital display panel together with their confidence value. The confidence value tends to go down with improper alignment, eye movement, drooping eye lashes, small pupils, and opacities of the media. Further operating and maintenance information is detailed in the instruction manual.

A total of 172 eyes in 90 patients (eight were one-eyed) were tested in a comparative analysis. Their ages ranged from 6 years to 75 years (Table 1). Except for 19 patients who were medical or paramedical staff all the subjects in this study were those attending the outpatient department of our hospital for refractive problems.

Determination of the refractive error in all the eyes was done clinically as well as on the AR, but not necessarily by the same examiner. When both the tests were conducted by the same person, the clinical refraction was invariably done first so as to obviate any possible examiner bias in the clinical refractive data.

All refractions on the AR were performed without the use of mydriatics or cycloplegics. The clinical refractions were done either similarly (manifest or dry) or, if necessary, under the effect of cycloplegics (homatropine 2% drops or atropine 1% ointment) or mydriatics (phenylephrine 10% drops), depending on the age of the patient, as is usual in clinical refractive practice. The final prescriptions were based on the objective clinical refraction data and the subjective acceptance by the patient, and the

prescriptions were then compared with the AR printout data.

Results on the AR with a confidence value of less than 90 were rejected. A minimum of three readings were obtained for each eye tested, and the reading with the maximum confidence value in each eye was selected for comparison. In those few eyes with two or three readings with identical confidence values the average of each component (sphere, cylinder, and axis) was taken into account. In some eyes not even one reading with a confidence value over 90 could be attained: these were rejected for the purposes of comparison.

The comparative data obtained on the AR and by clinical refraction were analysed for degree of agreement for various types and grades of refractive error and by age groups.

Results

Of the total number of 172 eyes tested the data from seven had to be discarded for the purposes of the comparative study, as an AR reading with a confidence value of over 90 could not be obtained in spite of repeated examinations. Thus the clinical and AR data in 165 eyes of 86 patients were finally compared and analysed. Their refractive error and distribution by age are depicted in Table 1. Of these 86 patients 47 were males and 39 females.

The mean difference and standard deviations (SD) in spherical equivalent data and cylindrical power and axis are depicted in Table 2. The comparative analysis for various types and grades of refractive error is given in Table 3 and the percentage agreement for different refractive components in Table 4.

The cylinder power data are shown in Tables 3 and 4 and the cylinder axis data in Tables 4 and 5. The variations of degree of agreement in the different age groups are recorded in Table 6.

When comparing the spherical equivalent data obtained clinically and by AR for the two eyes of the same patient we analysed the degree of aniso-

Table 2 Mean differences and standard deviations between auto refractometer and clinical refractive data (165 eyes)

	Spherical equivalent (D)	Cylinder power (D)	Cylinder axis (°)	Anisometropia* (D)
Mean	-0.58	-0.31	6.43	+0.13
SD	±0.79	±0.62	±9.85	±0.56

*The + sign indicates more anisometropia on NR-1000F than shown by clinical refractive data

Table 3 Degree of difference between the Auto Refractometer data and clinical refractive data for various refractive components in different types and grades of refractive error (165 eyes)

Refractive component	Emmetropia (30 eyes)			Myopia (79 eyes)									Hypermetropia (47 eyes)									Aphakia (6 eyes)			Mixed astigmatism (3 eyes)		
				Up to -3 D (67 eyes)			-3 D to -6 D (7 eyes)			>-6 D (5 eyes)			Up to +3 D (42 eyes)			+3 D to +6 D (3 eyes)			>+6 D (2 eyes)								
	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
Sphere component	20	4	6	41	18	8	1	6	0	4	0	1	19	12	11	1	1	1	1	0	1	3	3	0	2	1	0
Cylinder component	19	7	4	47	14	6	5	2	0	2	3	0	24	12	6	2	0	1	0	1	1	2	2	2	2	1	0
Spherical equivalent	16	5	9	33	16	18	2	1	4	4	1	0	17	8	17	2	1	0	0	2	0	4	1	1	3	0	0
Mean	-0.53			-0.63			-0.68			-0.37			-0.77			+0.24			0			+0.39			+0.01		
S.D.	±0.79			±0.66			±0.57			±0.46			±0.91			±0.90			±0.50			±0.68			±0.44		

I: Difference less than or equal to 0.50 D

II: Difference more than 0.50 D up to 1.00 D.

III: Difference more than 1.00 D

Table 4 Percentage agreement between auto refractometer data and clinical data of various refractive components (165 eyes)

Spherical equivalent (D)		Sphere component (D)		Cylinder component (D)		Cylinder axis		
±0.50	±1.00	±0.50	±1.00	±0.50	±1.00	Equal to or under 10°	More than 10°	No cylinder in one of the testings
52%	70%	56%	84%	61%	86%	37%	25%	38%

Table 5 Degree of agreement of cylinder axis between auto refractometer and clinical refractive data in different types and grades of refractive error (165 eyes)

	Emmetropia	Myopia			Hypermetropia			Aphakia	Mixed astigmatism
		Up to -3 D	-3 D up to -6 D	Equal to or more than -6 D	Up to 3 D	3 D up to 6 D	Equal to or more than 6 D		
Cylinder axis within 10°	7	28	4	1	16	1	0	2	2
Cylinder axis difference >10°	1	21	3	4	9	0	0	3	1
No cylinder in one of the testings	22	18	0	0	17	2	2	1	0
Total (165 eyes)	30	67	7	5	42	3	2	6	3

Table 6 Degree of difference between auto refractometer data and clinical refractive data for various age groups in different types of refractive error (165 eyes)

Age in years	<10 (6 eyes)			11 to 20 (60 eyes)			21 to 30 (51 eyes)			31 to 40 (20 eyes)			41 to 50 (10 eyes)			More than 50 (18 eyes)		
	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
Sphere component	3	2	1	39	16	5	24	15	12	7	9	4	9	1	0	13	4	1
Cylinder component	3	3	0	38	15	7	29	14	8	8	6	6	6	2	2	11	4	3
Spherical equivalent	4	0	2	29	18	13	20	9	22	8	3	9	6	1	3	14	3	1
Mean	-0.74			-0.49			-0.82			-0.87			-0.50			+0.15		
S.D.	±0.74			±0.71			±0.82			±0.79			±0.54			±0.48		

I: Difference less than or equal to 0.50 D.

II: Difference more than 0.50 D up to 1.00 D

III: Difference more than 1.00 D.

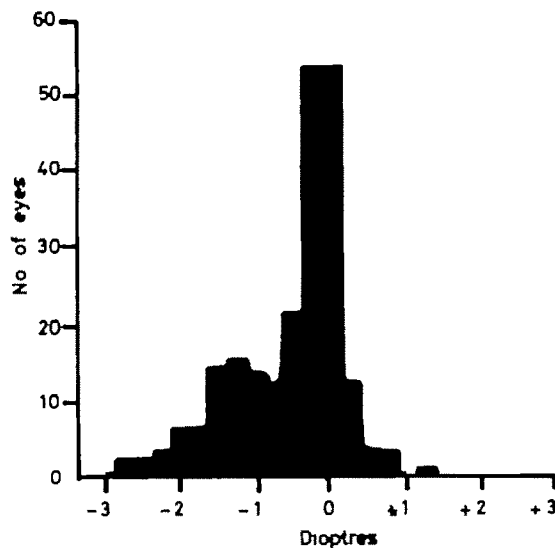


Fig. 1 Spherical equivalent values of 165 eyes: a comparison between NR-1000F and clinical refractive data.

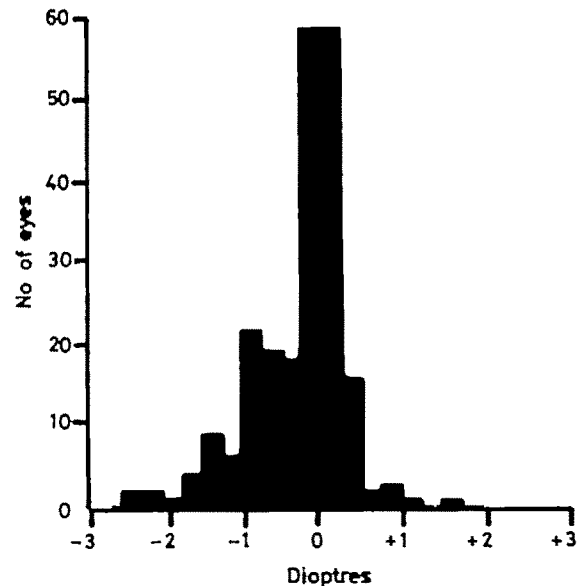


Fig. 2 Sphere component values of 165 eyes: a comparison between NR-1000F and clinical refractive data.

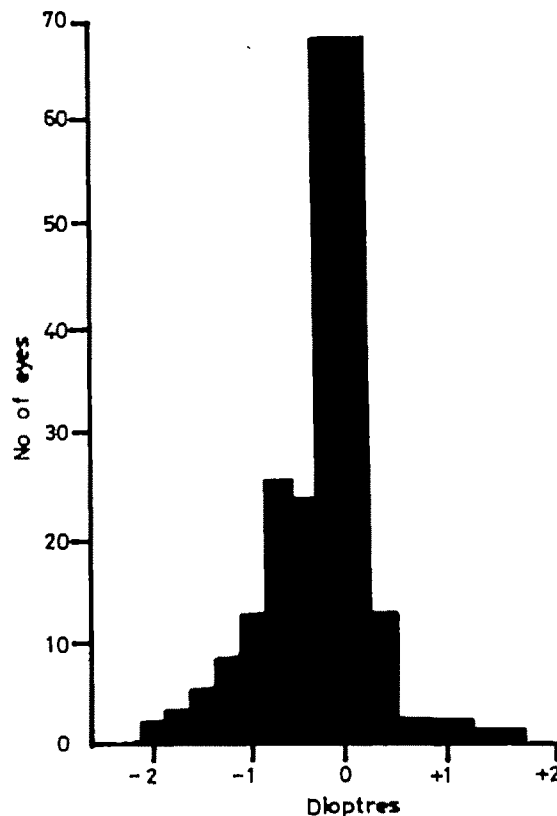


Fig. 3 Cylinder power data of 165 eyes: a comparison between NR-1000F and clinical refractive data.

metropia by each method. It was found that the mean difference was $+0.13$ D ($SD \pm 0.56$ D), the $+$ sign here indicating a greater amount of anisometropia for AR data than clinical refractive data. Interestingly, a 'reversal' in anisometropia was noted in 10 of our 79 cases where both eyes were tested, that is, clinical data showed more plus for one eye and AR data more plus for the other eye.

Discussion

In our study eyes with a confidence value reading of less than 90 as indicated on the AR printout were rejected for the purposes of comparative analysis. Examiner bias was obviated by the methods detailed earlier.

It is evident from Figs. 1 and 2 and Table 2 that the AR recordings are, by and large, skewed strongly towards more minus or less plus than our clinical refractive data. It is also obvious from Table 3 that this skew deviation towards greater minus is more

In Figs 1-3 the abscissa denotes the various degrees of dioptric difference observed between the AR and clinical refractive data, plotted against the corresponding number of eyes shown on the ordinate. The $+$ sign in the abscissa signifies that the AR reading was more hypermetropic (or less myopic) than that of the clinical refraction, and the $-$ sign indicates that the AR reading was more myopic (or less hypermetropic) than that of the clinical refraction. Note that the AR recordings skew towards more minus (or less plus) than our clinical refractive data.

pronounced in the patients with emmetropia, low myopia (up to -3 D), and low hypermetropia (up to $+3$ D). The minus error tends to come down in the higher myopic and hypermetropic groups, though the number of eyes in these groups is understandably small, as is only to be expected in a standard population sample. The reason for this difference seems obvious, namely, eyes with emmetropia or low refractive errors were capable of a fair degree of accommodation which the in-built automatic fogging system of the NR-1000F failed adequately to neutralise. The declining percentage of eyes showing higher minus error on comparison (more than -1 D) with increasing age over 40 years (Table 6) also supports this view of incomplete accommodative neutralisation on AR, since the reduced capacity of accommodation with increasing age obviously tends to reduce this error. That the minus error in the few aphakic patients tested was significantly lower corroborates our explanation. For obvious reasons patients with higher refractive errors did not wish to accommodate significantly, and therefore the minus error recorded was much less in these eyes (Table 3).

It thus seems that an objective refractometer like NR-1000F would be far more accurate in aphakic patients and those with high refractive errors, but much less reliable in emmetropes and those with low refractive errors, especially in younger patients. The agreement of AR with clinical refractive data was very good in the three cases of mixed astigmatism tested (Tables 3 and 5); it is well known that such eyes hardly tend to accommodate so as to maintain the retinal image at or about the circle of least diffusion.

Variation in our results as compared with those of other studies may be partly attributable to basic differences in the methods of analysing the data. Our system of segregating eyes into graded refractive error groups and age groups seems to be a far more critical method of analysis than previous workers have used.

Evaluation of this type has been attempted to some extent earlier⁸ on a subjective refractor (SR III), but no comments are available on the distribution by age. Subjects below the age of 20 were not included in that analysis,⁸ and in another study⁹ no information on the age of the patients was given. It has also been suggested⁸ that the inclusion of younger subjects would lower the extent of agreement between clinical and automatic refractions, and in order to evaluate the effect of overaccommodation on their SR III refractive data a study involving a large number of younger subjects would be needed.⁸ Our analysis has included 66 eyes of patients under 20 years of age, and the results of these have certainly borne out the suspicions harboured by previous workers.⁸

On clinical refractive assessment 123 out of 165 eyes (74.5%) showed no cylindrical error, whereas only 24 eyes (14.5%) showed purely spherical error on the AR. It seems that the cylindrical values obtained on the AR may often not be of clinical significance in many eyes.

The value of the cylindrical component obtained on the AR, like those for the spherical component and spherical equivalents, are also skewed towards more minus or less plus when compared with clinical refractive data (Fig. 3, Table 2). This observation has also been made earlier on the SR III subjective refractor.⁸ Again, like the spherical data, the skew deviation for cylinder power towards greater minus is more pronounced in emmetropic, low myopic, and low hypermetropic groups. The difference in agreement between the AR and clinical data on the cylindrical component in the various age groups (Table 6) was not significant. This is to be expected, as the cylindrical power in a given eye is unlikely to be influenced by accommodative effort, in contrast to the spherical component.

The mean difference of cylinder axis values determined clinically and on the AR was 6.43° (Table 2) with a standard deviation of $\pm 9.85^\circ$. The determination of axis by the AR appears to be quite reliable and accurate. Similar observations have been made before,⁸ though on a subjective refractor axis readings were found to vary in the same eye on separate testings. The reliability of the NR-1000F for cylinder axis determination seems to be greater than its accuracy in recording the spherical and cylindrical powers.

Our comments on the anisometropic data and 'reversal' in anisometropia are in fair agreement with the earlier observations by Perrigin *et al.*⁸ These should be kept in mind while clinically prescribing on data obtained by automatic refractors, subjective or objective.

In seven of the total of 172 eyes in our study the recommended confidence value of over 90 could not be obtained despite repeated efforts by the patient as well as the examiner, without there being any apparent reason. Conversely, a higher confidence value rating on the AR did not always prove more reliable than the figures obtained with a lower confidence value, when compared with the clinical refractive data for that eye. The reason for this is not clear. The operating manual supplied with the NR-1000F also comments on this apparent paradox, though no explanation is suggested.

It must be pointed out that the AR has proved to be extremely useful in the odd eye where retinoscopy and clinical improvement proved most unsatisfactory, especially in those eyes with corneal opacity.

We suggest that automatic refractometers like the

NR-1000F have a place in busy ophthalmic clinics, such as in a large hospital, and should be handled by trained operators to give baseline refractive data. The AR reading should not be prescribed straight away without carefully checking the acceptance subjectively, or using it as a guideline in case the clinical refraction presents difficulties. Automatic refractors are doubtless an invaluable aid to the specialist, but they do not and should not replace the art of clinical refraction.

Inadequate neutralisation of the patient's accommodative efforts by the in-built automatic fogging system of the NR-1000F appears to be the major drawback of this objective autorefractometer. It is possible that in spite of the fogging system the fixation target still induces a significant degree of instrument myopia. Further work is being carried out on the AR with eyes under the effect of cycloplegics.

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Subconjunctival emphysema due to trauma by compressed air tube

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SUMMARY A rare case of subconjunctival emphysema due to trauma by compressed air tube, without fracture in the orbit, and its treatment are described.

An orbital fracture is a common complication of trauma to the eye. One of the classical signs of such a fracture is the presence of subconjunctival emphysema as a consequence of direct passage of air from the nasal sinuses to the orbit.^{1,2} We have treated a patient who suffered from subconjunctival emphysema after trauma due to direct penetration of compressed air to the orbit, without orbital fracture. We believe this type of ophthalmic injury has not been described previously.

Case report

A 29-year-old male was wounded in his left eye while working in a metal factory. He was cleaning himself from metal dust, using a compressed air tube, at 50 psi (3.5 kg/cm², approx. 3 atmospheres), when his left upper eyelid was everted by the pressure and the

air stream wounded his eye. On examination the visual acuity was normal in both eyes. The left eye had a large subconjunctival emphysema (Fig. 1), with a small metal foreign body in the cornea. The intraocular pressure was 28 mmHg by applanation tonometry, but the inner parts were normal. An x-ray showed that air had collected around the cornea (Fig. 2) without an orbital fracture.

Early treatment included the removal of the foreign body from the cornea and the bandaging of the eye with antibiotic ointment. The following day most of the air in the upper part was absorbed, while the emphysema persisted in the lower conjunctiva and prevented lid closure. An incision was made in the conjunctiva to release the air. Three days later the patient had completely recovered.



Fig. 1 Severe subconjunctival emphysema.



Fig. 2 Subconjunctival emphysema (arrow) in the form of a ring around the cornea. There is no sign of an orbital fracture.

Discussion

This rare type of trauma resulted in emphysema by direct penetration of air through the thin conjunctiva. We believe that the high pressure created some microscopic tears in the conjunctiva, but these tears closed immediately afterwards, resulting in emphysema. The air was spontaneously absorbed in a few days, but the patient's inability to close the lids justified surgical drainage.

In the classical ophthalmological textbooks the presence of a subconjunctival emphysema after orbital trauma is considered to be pathognomonic of

an orbital fracture.^{1,2} The only information dealing with subconjunctival emphysema without an orbital fracture is to be found in an article on deep diving.³

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Morning glory syndrome: clinical and electrofunctional study of three cases

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SUMMARY Three cases of morning glory syndrome are described and some new electrofunctional and tomodesitometric findings are reported. The amplitude of the waves of the electroretinogram is reduced and correlates with the extension of the retinal changes. The visually evoked potentials elicited with bright flashes have normal latencies but generally subnormal amplitudes. The amplitude of the potentials probably depends on the degree of involvement of the optic nerve. The computerised tomography performed in one patient disclosed undescribed changes in the retrobulbar optic nerve.

The term morning glory syndrome was given by Kindler¹ in 1970 to a rare ocular anomaly characterised by a large staphylomatous optic disc covered by glial tissue. The peripapillary area is occupied by a ring of pigmentary abnormality and crossed by anomalous retinal vessels.

During the last few years many cases of morning glory syndrome have been described. These reports have contributed to the clarification of various clinical,^{2–4} pathogenetical,^{5–7} and pathological problems of the disease. The electrophysiological features, however, have not been extensively investigated. For this reason we are reporting three new cases of morning glory syndrome studied particularly from the electrofunctional point of view.

Materials and methods

The electroretinogram was recorded after dilatation of the pupils with 0.5% tropicamide and 10% phenylephrine. The active electrode was a Burian-Allen silver electrode; the indifferent electrode was placed on the eyebrow and the ground in the centre of the forehead. The scotopic electroretinogram was recorded after 15 minutes of dark adaptation. The stimulation was a single flash of white light emitted by a photostimulator placed 33 cm away from the patient's forehead. The intensity of stimulation was of 0.3 Joule/flash. This intensity was attenuated by

the use of neutral density filters of 3 and 2 logarithmic units. The photopic electroretinogram was recorded after 5 minutes of light adaptation at 1000 lux. The frequency of stimulation was 20 and 50 flashes/second with light intensity of 0.2 Joule. The signals were led to an OTE Biomedica preamplifier Model 1076 with a time constant of 0.3 second. For the photopic electroretinogram 64 responses were averaged by an OTE Biomedica neuroaveraged Model 1172. The responses were written by an X–Y recorder OTE Biomedica Model 1013.

The visually evoked potentials were recorded in mesopic adaptation and mydriasis with a needle electrode inserted 2.5 cm above theinion. The indifferent electrode was placed on the vertex; the ear lobe was earthed. The stimuli were flashes of white light emitted by a photostimulator placed 33 cm away from the patient, the intensity being 0.3 Joule and the frequency 1 per second, and flashes of sinusoidal light with frequency of 10 and 20 per second. The responses were amplified, and the time constant was of 0.7 second. For each stimulus 80–100 responses were evoked that were subsequently averaged and recorded.

The Kowa RC–xV retinograph was employed to take the fundus photographs and the fluorescein angiography after the injection of 5 ml of 10% sodium fluorescein into a superficial vein of the forearm. The visual field was checked with the Goldmann perimeter. The colour sense was tested with the pseudoisochromatic tables of Ishihara.

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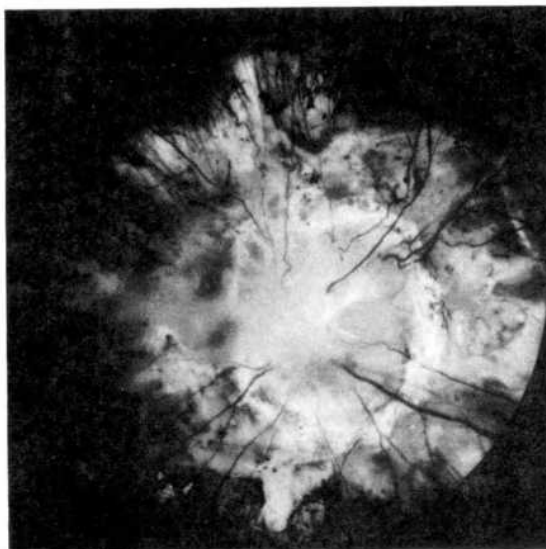


Fig. 1 Case 1. Fundus photograph of the left eye showing an enlarged and staphylomatous optic disc covered by a mass of greyish tissue and surrounded by a ring of retinochoroidal atrophy.

Case reports

CASE 1

A 31-year-old man was referred to our clinic with a diagnosis of coloboma of the optic nerve in the left eye. He had never seen well with this eye. Corrected visual acuity was 20/20 in the right eye with sph + 2.00 and uncertain light perception in the left eye. The refractive error in the left eye was of -2.50 dioptres. The right pupil was normally responsive to light. The left pupil had a diameter of 3 mm and an afferent pupillary defect. The left eye had exotropia of 45 prism dioptres and pendular nystagmus. The ocular adnexa, the anterior segment, the vitreous, and the intraocular pressure were normal.

The right fundus showed optic disc pallor with superior and inferior arcuate nerve fibre bundle defects. In the left eye the optic disc was enlarged, staphylomatous, and partly covered by a mass of greyish tissue (Fig. 1). From the centre of the disc arose a number of straight and thin retinal vessels. The optic nerve head was surrounded by a large area of retinochoroidal atrophy speckled by small amounts of pigment. Below the disc there was a small retinochoroidal coloboma. The macula was unrecognisable.

Fluorescein angiography gave normal results in the right eye and in the left showed early visualisation of the choroidal vessels due to the atrophy of the peripapillary pigment epithelium. The filling of the retinal arteries and veins was delayed. Some vessels showed a tortuous course and loops, and some

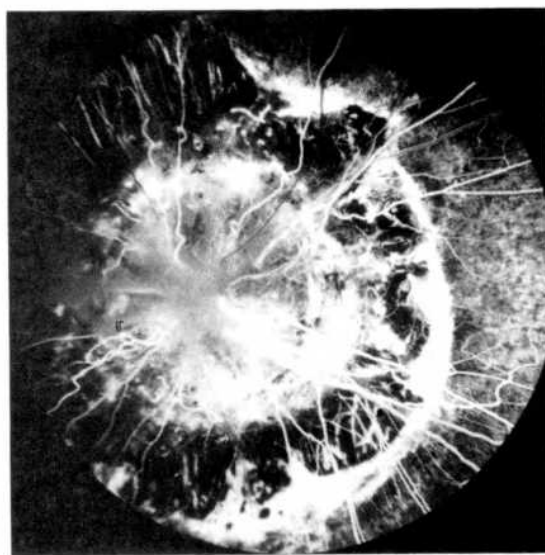


Fig. 2 Case 1. Fluorescein angiography of the left eye, early venous phase. The vessels on the disc appear anomalous and the filling of the venules is delayed (25 seconds). Temporally to the disc the macula is unrecognisable.

leakage was observed (Fig. 2). In the late venous phase the walls of the staphyloma became hyperfluorescent (Fig. 3).

Goldmann visual field revealed a nasal hemianopia in the right eye (Fig. 4). This defect was identical to the one found in an earlier examination made six

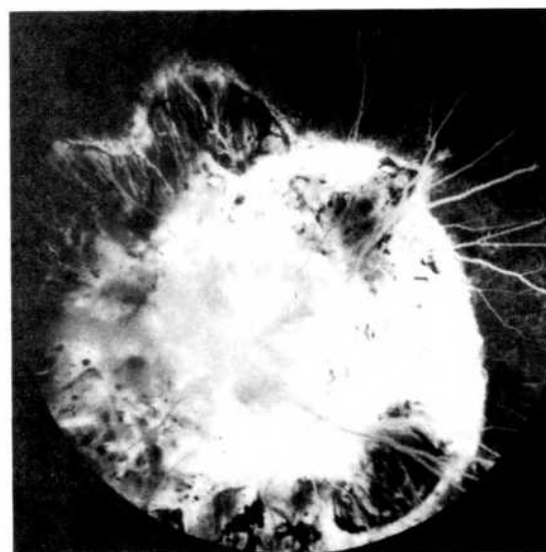


Fig. 3 Case 1. Fluorescein angiography of the left eye, late venous phase. The peripapillary area and the walls of the staphyloma are hyperfluorescent.

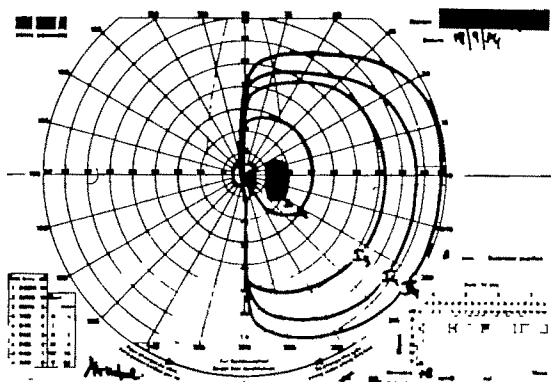


Fig 4 Case 1 The visual field of the right eye shows a nasal hemianopia

years before. The visual field of the left eye was impossible to chart, but the patient seemed to perceive faintly the target V_4 from the nasal side. Colour sense was normal in the right eye and not recordable in the left eye.

The electroretinogram and the visually evoked potentials were unremarkable in the right eye. In the scotopic electroretinogram of the left eye the amplitudes of the a and particularly of the b waves were subnormal (Fig. 5). The implicit times were normal.

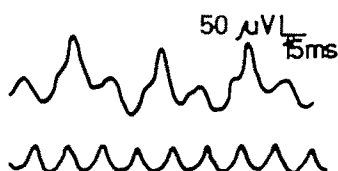
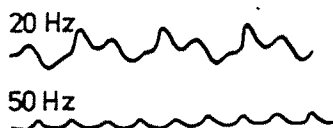
Scotopic ERG



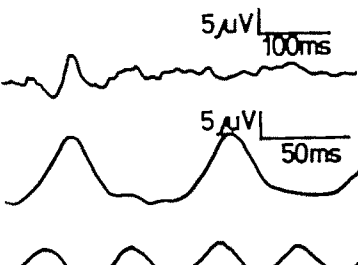
200 μ V | 30 ms



Photopic ERG



VEPs



The amplitude of the photopic electroretinogram was also pathologically reduced. The visually evoked potentials elicited at 1 Hz had a borderline latency and amplitude. At higher frequencies the amplitude of the potentials was frankly abnormal (Fig. 5). The electrofunctional responses of the three patients with morning glory syndrome are summarised in Table 1.

Computerised tomography with contrast of the left orbit showed a high density intrabulbar optic nerve. The retrobulbar optic nerve was thickened (Fig. 6). The peripheral portion of the nerve was hypodense and a core of hypodensity was present in a long tract of the nerve (Fig. 7). Cerebral CT showed porencephaly of the right parieto-occipital lobe

CASE 2

This 21-year-old man complained of very low visual acuity in his right eye since birth. The visual acuity was 2/200 in the right eye and 20/20 in the left eye with sph -1.00 cyl -1.00 ax 90° . In the right eye the refraction was of sph -3.50 cyl -1.25 ax 90° . There was a marked afferent pupillary defect in the right eye. Ocular motility, anterior segment, lens, and vitreous were normal in both eyes.

Fundus examination of the right eye showed a large and excavated disc surmounted by a tuft of white matter hiding the origin of the retinal vessels. These vessels were numerous, straight, and of

Fig 5 The electroretinogram and the visually evoked potentials of the left eye of patient 1 (on left) compared with the responses of a normal subject (on right)

Table 1 Summary of the electroretinograms and the visually evoked potentials

Electroretinogram								
	Scotopic 3	Scotopic 2	Scotopic 0		Scotopic 0		Photopic 20	Photopic 50
	b Wave amplitude	b Wave amplitude	a Wave amplitude	b Wave amplitude	a Wave implicit time	b Wave implicit time	Amplitude	Amplitude
Case 1	57 μ V	125 μ V	125 μ V	37 μ V	38 ms	69 ms	90 μ V	28 μ V
Case 2	87 μ V	200 μ V	175 μ V	125 μ V	34 ms	65 ms	119 μ V	41 μ V
Case 3	50 μ V	137 μ V	150 μ V	137 μ V	38 ms	67 ms	162 μ V	25 μ V
Normal	132 $\pm$ 43 μ V	330 $\pm$ 72 μ V	265 $\pm$ 63 μ V	226 $\pm$ 55 μ V	34.6 $\pm$ 2.5 ms	64.9 $\pm$ 4.5 ms	171 $\pm$ 25 μ V	72 $\pm$ 19 μ V

Visual evoked potentials				
	1 Hz	1 Hz	10 Hz	20 Hz
	Wave amplitude	Wave latency	Amplitude	Amplitude
Case 1	4.5 μ V	114 ms	5.75 μ V	1.5 μ V
Case 2	—	—	4.5 μ V	1.75 μ V
Case 3	7.5 μ V	104 ms	11 μ V	—
Normal	8.3 $\pm$ 2.5 μ V	101 $\pm$ 11.7 ms	12.9 $\pm$ 3.1 μ V	6.8 $\pm$ 1.7 μ V

uniform calibre (Fig. 8). A prominent ring of pigmentary changes occupied the peripapillary area. The macula was hypoplastic and without reflex. The fundus of the left eye was normal.

In fluorescein angiography the retinal arteries were filled about 2 seconds after the choroidal arteries visible through the peripapillary pigment defect. The epipapillary glial mass caused a masking hypofluorescence of the optic disc. The retinal veins were filled 8

seconds after the arteries. In the late angiograms the peripapillary area and the walls of the staphyloma were slightly hyperfluorescent. The retinal vessels never leaked fluorescein (Fig. 9).

The visual field of the right eye delineated a dense central scotoma. None of the Ishihara tables were recognised in this eye.

The amplitudes of the waves of the scotopic and the photopic electroretinogram were subnormal in



Fig. 6 Case 1. Computerised tomography, sagittal view. The left intrabulbar optic nerve is hyperdense (arrow), and the retrobulbar nerve appears enlarged.

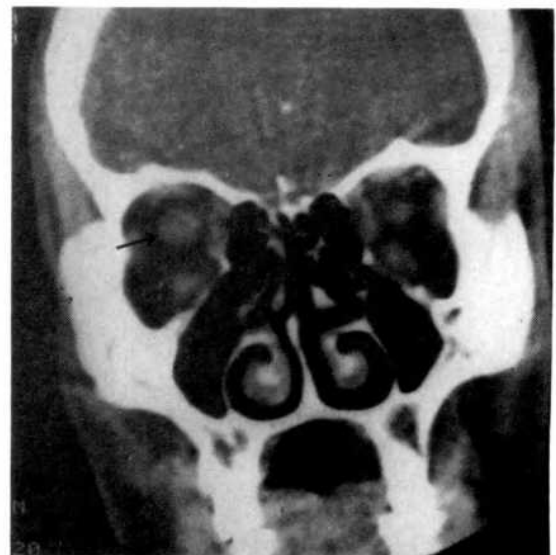


Fig. 7 Case 1. Computerised tomography, coronal view. Delineates hypodense areas around and inside the left retrobulbar optic nerve (arrow).

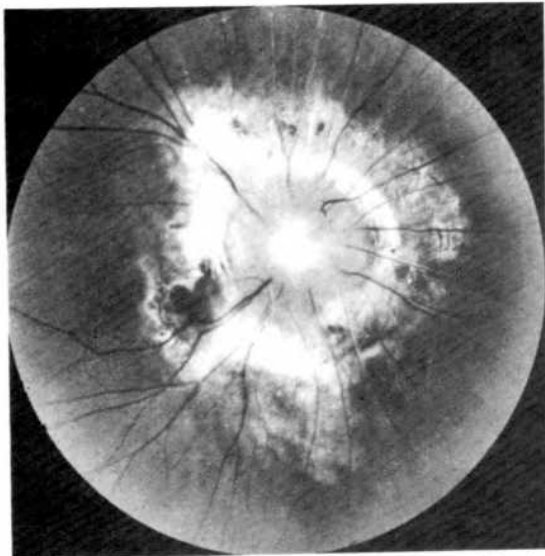


Fig. 8 Case 2. Fundus photograph of the right eye. The disc is enlarged and surmounted by a tuft of glial tissue. The retinal arteries are straight and sheathed.

the right eye (Fig. 10). This amplitude reduction involved the a as well as the b wave. The implicit times were normal. It was not possible to record visually evoked potentials at 1 Hz. At 10 and 20 Hz the potentials had very low amplitudes (Fig. 10). In the left eye the electroretinogram and the visually evoked potentials had normal values.

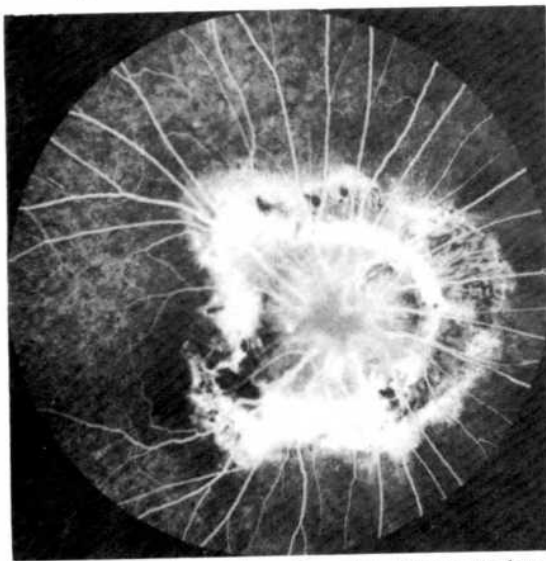


Fig. 9 Case 2. Fluorescein angiography, late venous phase. The anomalous vessels do not leak dye. The fovea is barely recognisable and partly covered by the ring of pigmentary changes.

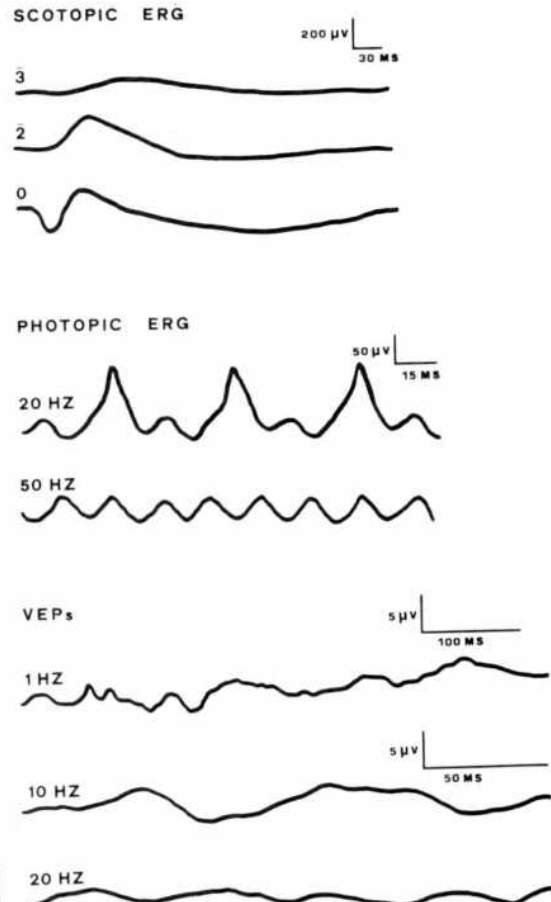


Fig. 10 Case 2. Electroretinogram and visually evoked potentials of the right eye.

CASE 3

A woman of 73 years was referred to us to have her cataracts examined. She had had no previous ocular troubles and remembered that she could see well with both eyes when she was young. She suffered from slight diabetes. Her visual acuity was 20/400 in the right eye and 20/200 in the left eye with cyl -1.00 ax 90°. The right eye was emmetropic. Pupillary responses were normally present in both eyes. Examination of extrinsic motility disclosed a slight hypofunction of the superior oblique of the left eye. There were bilateral nuclear cataracts.

In the right eye the optic disc was slightly enlarged and staphylomatous and a white spot of tissue of glial appearance lay in its centre. The retinal vessels had a straight course at the origin but were easily distinguishable in arteries and veins. A wide pigmentary defect surrounded the disc. The macula appeared normal (Fig. 11). The fundus of the left eye showed

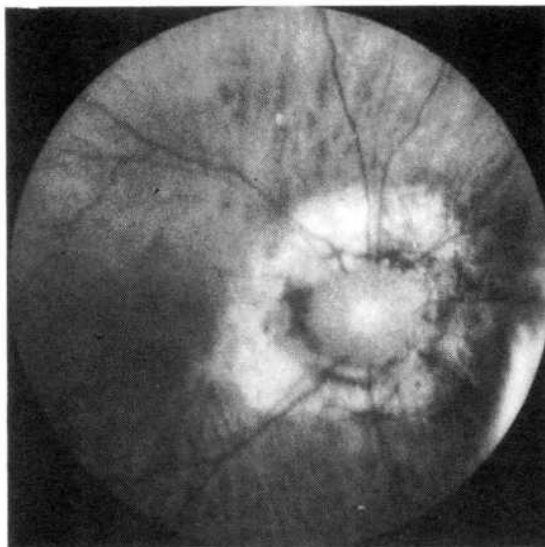


Fig. 11 Case 3. Fundus photograph of the right eye showing a slightly enlarged optic disc with a peripapillary ring of pigment atrophy. The arteries are easily distinguishable from the veins. The low quality of the photograph is due to the cataract.

only a diffuse senile atrophy of the retinal pigment epithelium.

In fluorescein angiography the peripapillary atrophic area had been hypofluorescent from the early phase. The filling of the retinal vessels was

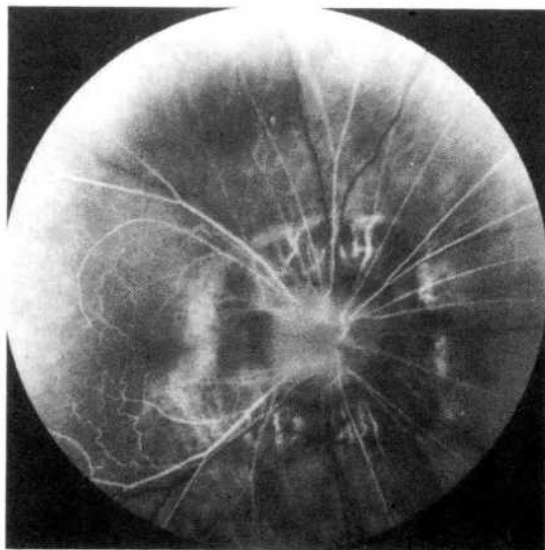


Fig. 12 Case 3. Fluorescein angiography, early venous phase. The choroidal vessels are visible through the peripapillary defect. The filling of the veins is delayed (18 seconds). The macular area is well delineated.

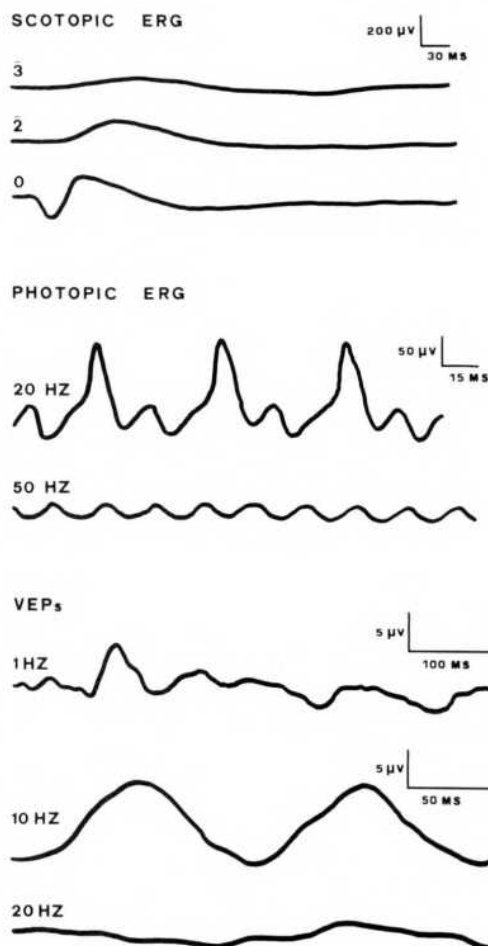


Fig. 13 Case 3. Electroretinogram and visually evoked potentials of the right eye.

delayed. The macula showed a normal fluorescence (Fig. 12).

The visual field was similar in both eyes, showing constriction of the peripheral isoptres and absence of the central ones. The colour sense was normal.

In the right eye the scotopic and photopic electroretinogram was subnormal with almost all the stimuli (Fig. 13). The amplitude of the visually evoked potentials was normal at least at low frequencies (Fig. 13). The latency at 1 Hz was normal. In the left eye the electroretinogram was at low limits; the visually evoked potentials were normal.

Discussion

The ophthalmological features of the morning glory syndrome are well known.^{18,9} The enlarged optic disc lies in the centre of a staphyloma involving the nerve

and the peripapillary area of the globe, so that the region assumes a funnel-shaped appearance. Glial proliferation on the disc can be considerable and cause progressive elevation of the optic nerve head. In the peripapillary area a ring of pigmentary disturbance is almost constant. The retinal vessels arising from the optic disc are numerous, straight, and hardly distinguishable between arteries and veins.

The cases reported here show all these features to a different extent. In the first patient the disc is much enlarged, but in the third case it is of an almost normal dimension. Gliosis is remarkable in the first case, where it spreads in finger-like projections towards the retina. There are atrophic peripapillary pigmentary changes in all cases, while there is little hyperplasia. The retinal vessels are very anomalous and rich in loops in the first case, but far less abnormal in the third.

Macular abnormalities are frequent in the morning glory syndrome. Sometimes the foveal reflex is lacking and a yellowish retinal area temporal to the peripapillary ring represents an abnormally developed macula.³ At other times the macula shows a normal development, and a satisfactory visual acuity can be recorded.¹⁰ In case 1 a structure similar to the macula is lacking, while it is present but rudimentary in case 2, where the macula appears somewhat pigmented, stretched towards the disc, and without a foveal reflex. In case 3 the macula is normal, and it is probable that the low visual acuity is due more to the cataract than to the fundal anomaly.

Orbital computerised tomography of the only patient in which this examination was performed showed undescribed findings. In the previous tomodensitometric reports of the morning glory syndrome the retrobulbar optic nerve was normal except at its distal end, where the staphyloma could be delineated.^{2,7,11,12} In our case the retrobulbar part of the nerve was thickened: a hypodense sheath surrounded the nerve proper and a hypodense core was encased axially in the optic nerve. Several pathological studies showed that the retrobulbar optic nerve is highly abnormal in the morning glory syndrome. The nerve is atrophic and the meningeal sheaths are replaced by fibrous and fatty tissue.^{7,13} In particular, the pathological specimen from case 2 described by Apple *et al.*¹⁴ evokes the tomodensitometric picture reported here: the optic nerve showed a perineural sheath of adipose tissue, and foci of adipose tissue were located centrally in the nerve. Thus the hypodense matter located inside and around the optic nerve in our case might be adipose tissue migrated into the optic nerve through the embryonic fissure¹⁵ or produced by adipose metaplasia of the perioptic tissues.¹⁴

In case 1 there is a nasal hemianopia in the visual

field of the contralateral eye. The defect was probably congenital and was unchanged after a lapse of six years. It was caused by the porencephaly of the ipsilateral posterior cerebral hemisphere. The optic atrophy and the nerve fibre bundle defects of the right eye were produced by the transsynaptic degeneration of the pregeniculate pathway.

In patients with morning glory syndrome many anomalies have been described in the involved eye, such as ciliary body cyst,¹ congenital cataract,¹⁶ persistent pupillary membrane,¹⁶ and vitreous cyst⁷; in the contralateral eye, congenital cataract,¹ anterior chamber cleavage syndrome,¹ microcornea,¹⁶ and Duane's retraction syndrome¹⁷; and in other systems, cleft palate and basal encephalocele,^{18,19} renal hypoplasia,²⁰ and somatic anomalies due to breaks of chromosomes.² Thus the morning glory syndrome may represent more than a simple optic nerve anomaly, a disembryogenetic disease with the involvement of various organs.

The electrofunctional findings of the morning glory syndrome are not well known. In one case of the syndrome with cataract²¹ the photopic electroretinogram was present, but the waves were less wide than contralaterally. The visually evoked potentials showed waves of little amplitude and badly individualised. In another study carried out in an eye with morning glory syndrome and without light perception⁹ the amplitude of the a and b wave of the electroretinogram was subnormal and the visually evoked potentials unrecordable.

The electroretinographic responses obtained from our patients confirm the scanty data of the literature. In all our three cases we recorded an electroretinogram of reduced amplitude. This abnormality concerns above all the b wave, and it is generally proportional to the retinal damage ophthalmoscopically visible. Histopathological studies performed on eyes affected by morning glory syndrome have shown that the retina is much involved. There is attenuation of the outer nuclear layer together with a localised absence of the visual cells,²² extensive areas of necrosis and cellular infiltration in the outer retinal layers,¹³ and glial cells replacing the ganglion cell layer.⁷

Such changes are prominent in a more or less wide peripapillary area. The rest of the retina may show some generalised atrophy, but the retinal layers appear to be normally formed and clearly recognisable. These facts well explain the electroretinographic findings—that is, the reduced amplitude of the waves and the normal implicit times. In fact amplitude and implicit time behave independently of one another in the localised diseases of the retina.²³ In these cases the amplitude is reduced because of the focal compromise of the retinal cells, but the implicit

time is normal owing to the normal transmission of the nervous impulse in the remaining healthy retina.

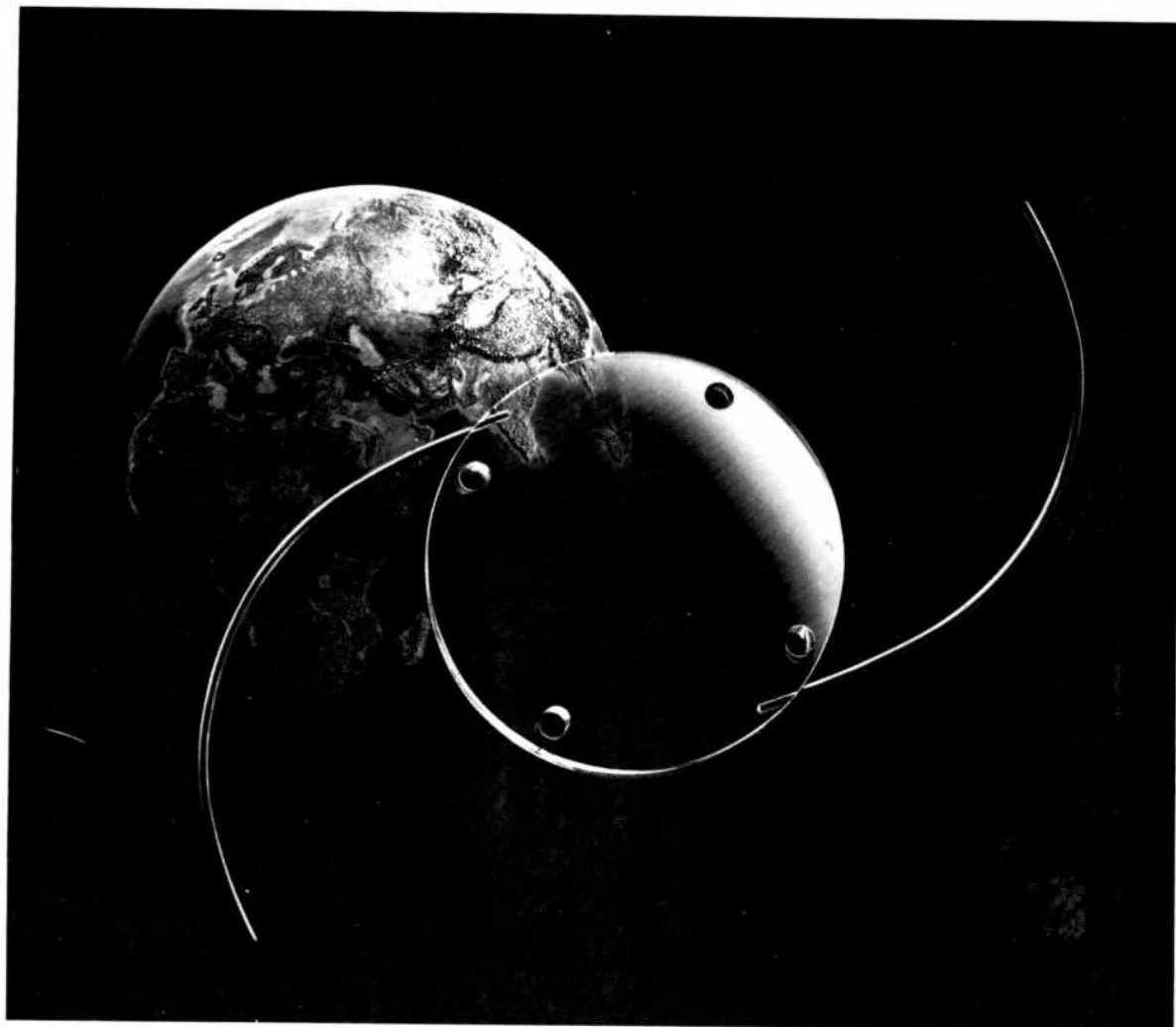
The visually evoked potentials are generally recordable but of subnormal amplitude in congenital anomalies of the optic disc.²⁴ The latency is usually normal. Our findings on patients with morning glory syndrome agree with the ones on patients with other anomalies of the optic disc. It was possible to elicit visually evoked potentials in all the patients, including the one with uncertain light perception. The amplitude of the potentials is much reduced in two cases, and it probably depends on the large reduction of fibres in the optic nerve. The axons may be almost totally replaced by glial cells, fibrosis, and calcifications.²⁵ Possible macular abnormalities may contribute to the reduced amplitude of the waves. The temporal components of the visual potentials were normal in all the cases in which a readable recording was obtained. Finally it should be emphasised that some of the abnormalities of the visually evoked potentials may arise from the strabismic amblyopia developing precociously in many cases of morning glory syndrome.

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Correspondence

Safety glasses only for boys?

SIR, We appreciate Tarkkanen and Tommila's reply¹ to our query² on their work. It appears that we did not, however, explain our intentions adequately.

Our concern is application of socioeconomic risk/benefit ratios in the prescription of glasses for safety reasons (we prescribe glasses with plastic lenses and plastic frames) for children and adults who have a permanent functional amblyopia in one eye. We agree with Tarkkanen and Tommila that this is a proper recommendation in principle because it protects the wearer from accidental trauma. And accidental trauma is the major single cause (61%),³ (45%)⁴ of loss of vision in the healthy eye in such patients.

On the other hand both adults and children and their parents innately and strongly resist the wearing of glasses even for this purpose. Peer pressure is a significant burden to the younger patient. Therefore we do not want to insist upon such safety glasses unless there is a real danger to the patient—i.e., a significant probability that such an accident may happen and cause the subject to be significantly visually handicapped per se. From the relatively greater risk of males to be traumatised it seemed possible that the probability of the loss of the better eye for a female patient in this situation might be so low that one would not be obliged to demand that they wear safety glasses.

Specifically, in Vereecken and Brabant's study⁴ of the 47 accidental traumatic loss cases 85% were male and 15% were female. (Our original query sought similar, additional data on this sex incidence.) Then from Tommila and Tarkkanen¹ we obtain an overall (trauma and disease) incidence of loss of the healthy eye of 1.75/1000 (actually 1.59/1000) persons with permanent amblyopia in one eye.

Calculations then show that, if the cause is trauma in 47% (from combining the data from both studies, (14+53) of (23+119)=67 of 142=47%) and the overall incidence of loss of the healthy eye is 1.59/1000, then the probability of loss from trauma is $47\% \times 1.59 = 0.75/1000$. If the male to female ratio is 85%/15%, respectively, for males this incidence is $85\% \times 0.75 = 0.635/1000$ and for females is $15\% \times 0.75 = 0.112/1000$.

In other words, when we prescribe safety glasses for such patients we are protecting the males from a 1 in 1575 chance of losing their good eye from trauma and the females from a 1 in 8929 chance.

We should also include in these calculations the likelihood of improvement of vision in the amblyopic eye spontaneously or with pleoptic treatment after loss of the better eye. Vereecken and Brabant⁴ found 28.5% improvement spontaneously or following pleoptic treatment. In fact 23% had a final visual acuity of 0.5 (20/40) or better; 21%, 0.6 (20/32); 17%, 0.7 (20/29) or better; and 7%, 0.8 (20/25) or better.

We usually consider 0.5 (20/40) not significantly handicapped because this vision in one eye qualifies for drivers licensing and almost all occupations. If we require one step better, 0.6 (20/32), to ensure that the individual is not permanently visually handicapped, then the 20% possibility of such recovery further reduces the odds of becoming

visually handicapped from trauma by 20%. Prescribing safety glasses then protects males from an approximately a 1 in 1900 chance and females from a 1 in 10 700 chance of becoming visually handicapped as a result of traumatic loss of their sole good eye.

Now since we cannot possibly protect everyone from everything, and even safety glasses do not protect the eye from trauma 100% of the time, what is our obligation in this regard?

One such benchmark in this regard was established several years ago when the principle of informed consent received so much attention. For complications which were not life threatening it was decided, admittedly quite arbitrarily, that if a complication occurred less frequently than 1:10 000 it could be considered such a chance occurrence that the physician was not obliged to inform the patient about it. If it is not necessary even to warn, then it should not be necessary to demand against such a chance occurrence. And the incidence of loss in this situation in females exceeds 1:10 000.

With regard to the economic cost/benefit ratio, a lifetime of wearing safety glasses is not an inconsiderable experience. If one purchases a new pair of glasses every five years for a reasonable cost of \$50.00 per pair, 10 pairs of glasses from age 5 to presbyopia at age 45 will cost \$500 per permanently amblyopic person. If only one in 10 000 are saved the loss of their good eye by constant wearing of such glasses, then it will cost $\$500 \times 10\,000 = \$5\,000\,000$ (5 million dollars) to save that one eye. Since such persons would probably not be totally blinded but only reduced to whatever vision they have in their permanently amblyopic eye, we may be talking about spending \$5 million to preserve only several lines on the eye chart for one patient.

In conclusion: there are three areas of consideration in recommending that persons with one permanently amblyopic eye wear safety type glasses to protect their remaining sound eye—namely (1) practical (patient acceptance), (2) social (as indicated by legal principles), and (3) economic. In all three areas there is significant support for a practice of not demanding safety glasses for females with one permanently amblyopic eye, rather for males only. Department of Ophthalmology, PAUL E ROMANO
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Book reviews

Guide to an Effective Outpatient Ophthalmic Surgical Center. Edited by STEPHEN P GINSBERG. Pp. 250. £37.75. SLACK: New Jersey. 1985

There can be few ophthalmologists working this side of the Atlantic who remain unaware of recent changes in the delivery of surgical care and the virtual imposition of outpatient ophthalmic surgery in the United States. The underlying reasons for change are less obvious, but in the American medical market place costs have escalated to a level unacceptable to the consumer and the reimbursement insurance agencies. The fundamental changes affecting surgical practice have to a large extent overtaken our American colleagues, prompting the publication of this manual aimed at the practitioner wishing to move with the times and establish his own outpatient surgical facility.

The editor has gathered together contributions from 26 authors wedded to the concepts and the practice of outpatient ophthalmic surgery. The introduction reviews briefly the history of outpatient surgery and sets out the advantages to the patient, the ophthalmologist, and society as a whole but with no mention of the possible disadvantages. The ground rules and basic requirements for establishing a personal surgical base are outlined, with the aim of a cost effective service, particularly for the care provider. The advice given to engage an experienced business consultant and simultaneously consult one's attorney and accountant neatly captures the ethos of many of the subsequent contributions. The remainder of the text deals with subjects as diverse as federal and state regulations, reimbursement and certification, and the construction and equipping of the multimillion dollar edifice. There are a number of interesting contributions concerning public relations and marketing, promotion of the service, and guidelines for the day-to-day running of the so-called ambulatory facility. An absorbing account is given of the medicolegal implications of outpatient surgery and that of professional liability, with some revealing statistics.

On first impression this manual would seem to have little to offer the British ophthalmologist working in the public or perhaps private sector. Many interesting issues are, however, raised, particularly in the areas of cost containment and budgeting as well as providing an insight into aspects of contemporary practice in the United States. A number of contributions are worth perusing and appear eminently relevant to the revised management structure of the National Health Service. Perhaps this book will ultimately become essential reading for those who elect to take on an extended managerial role or become a clinical budget holder.

R J COOLING

Atlas of Clinical Ophthalmology. By D. J. SPALTON, R A HITCHINGS, P A HUNTER. Pp. 331. £60.00. Churchill Livingstone. Edinburgh. 1984.

This extremely handsome volume is an introduction to clinical ophthalmology and an illustrated reference work. It is designed to show the type of clinical material encountered in general ophthalmic practice and the eye as a reflection of

disease elsewhere. It is beautifully illustrated, and it is nicely broken down into chapters on different aspects of eye disease, the format being basically the same throughout. On the whole the balance of the chapters is good, though some do contain more specialised details than others. I particularly liked the large numbers of pathology pictures alongside those of the clinical disease, and there are many x-rays, CT scans, ultrasound scans, and fluorescein angiograms where relevant. Another excellent feature was that parallel with any complicated photograph there was an accurate line diagram clarifying the more complicated features.

My only criticism of the book is the rather confusing layout of the print. It is arranged in two columns, and sometimes it is not clear when to switch from one to the other.

I would strongly recommend the book to all ophthalmologists, and despite its cost I consider it offers excellent value for money. It certainly should be purchased by all hospitals with eye surgeons in training.

RONALD J MARSH

Brain Mechanisms and Spatial Vision. Eds. DAVID J. INGLE, MARC JEANNEROD, DAVID N. LEE. Pp. 470. £44.50. Martinus Nijhoff: Dordrecht, Netherlands. 1985.

This book results from a NATO Advanced Study Institute held in June 1983. The aim was to provide a forum for discussion between workers concerned with perception and those interested in electrophysiology. The rapid advance in our understanding of the neurophysiology of vision following the work of Hubel and Wiesel has not been closely correlated with the behavioural output of given species of cortical detectors. The assembled 17 authors addressed themselves to these problems, and the book was edited by representatives from America, France, and Britain. The majority of papers were on aspects of visual perception and in particular depth perception, three dimensional vision, and their relations to movement. The opening chapter, on visual timing of interceptive action, discusses the visual aspects of catching a ball and the relationship of visual input to muscle skeletal co-ordination. Practical applications were studying the performance of crossing traffic and assessing the gaps between cars. Many papers contain mathematical and scientific data not relevant to the practising ophthalmologist. However, Cowey's paper on disturbances of stereopsis by brain damage is relevant, as is the paper by Jeannerod on the posterior parietal area as a spatial generator.

This book provides an update on recent neurophysiological and perceptual research, with a good bibliography at the end of each chapter. It is recommended to those with an interest in cerebral aspects of vision, but does not provide new avenues of benefit for our patients.

M D SANDERS

Everything You Need to Know About Your Eyes. By ROBERT YOUNGSON. Pp. 117. £2.50. Sheldon: London. 1985.

The nature and extent of misunderstanding and mythology about eyes and vision is so great that any effort to diminish them is to be welcomed. The number of texts devoted to this

end has recently multiplied, possibly owing to the widespread desire for further knowledge engendered among lay persons by the media. The present work covers the topic in an interesting and readable manner, and, while there are matters of emphasis with which there will always be some debate, the majority of topics are well and accurately covered. It is unlikely that the practising ophthalmologist will find himself at odds with what is stated. The language is appropriately non-technical, though the old difficulty of analogies of eyes with cameras, in this case a television camera, arises because one wonders in fact how many lay people do know how a camera works, let alone an electronic one.

Certainly this reviewer would be very happy to know that his patients had read this book, and perhaps even happier if he could be sure that the general practitioner and primary health care personnel had also done so. M J GILKES

Ophthalmology. 2nd revised edition. By FRITZ HOLLWICH. Pp. 363. DM 29.80. Georg Thieme Verlag: Stuttgart 1985.

This concise textbook of 363 pages provides an excellent basic introduction to ophthalmology. Despite its relatively small size it contains an immense amount of ophthalmic information, presented in a lucid and succinct manner and in an eminently readable form. The book is well organised, with introductory chapters on ocular and adnexal anatomy and physiology. Succeeding chapters systematically describe diseases of the various components of the eye, the ocular adnexae, and the orbit. Chapters are also devoted to glaucoma, strabismus, and disorders of the visual pathways, and useful sections are included on the eye and systemic disease and rehabilitation of the blind.

The information is clearly and logically presented and superbly illustrated by a wealth of line diagrams, schematic representations, and black-and-white photographs of quite exceptional quality. In addition, there are 73 colour figures which illustrate key ophthalmic disorders and occasionally form part of very informative and pertinent case presentations. The ophthalmic information is up to date, and modern therapeutic options and modalities are included in most chapters. Each chapter is followed by a short summary, and, although this is useful to some degree, there is considerable duplication of information, which is probably unnecessary in a book of this size.

In my opinion this is one of the best introductory ophthalmic textbooks and is ideally suited to medical students and those entering specialty training in ophthalmology. It is also enthusiastically recommended for general practitioners or physicians wishing to update their knowledge on current ophthalmic practice. DESMOND BARCHER

Cromwell's Glasses. By HOLLY KELLER. Pp. 28. £4.95. Julia MacRae: London. 1985.

Some of the simplest things give the greatest pleasure, and messages written in simple fashion tend to be more powerful. This little book for small children deals with the emotional problems of a young rabbit who has to wear

glasses. It is based on the premise that children who are myopic and do not have to wear glasses tend to be clumsy and unpopular, whereas once they wear glasses the world is all the better for them. As most ophthalmologists know, very many spectacles are inappropriately prescribed for children and often are only necessary for use in the classroom and only rarely for continual use. Clumsiness can rarely be ascribed to myopia.

While some of the rabbits drawn in the book looked like rabbits, the unfortunate victim rabbit, Cromwell, who is to have to wear glasses, had a bifid face (as did several of his relatives), and I suspect that this is due to the underlying brain malformation which accounted for the clumsiness and visual defect rather than a need for glasses.

The book is harmless, quite amusing, but not exactly a must for every paediatric ophthalmologist to have on the shelf of his waiting room.

DAVID TAYLOR

Virus Disease of the Eye. By D. L. EASTY. Pp. 350. £30.00. Lloyd-Luke: London. 1985.

This monumental work gives an authoritative, clear account of the types of virus that affect the eye, their structure, and the laboratory techniques used in their detection. There is a good account of the clinical conditions produced by the different viruses, and a comprehensive discussion of the possible mechanism by which the different clinical signs have been caused and the management of each clinical entity. The in-depth discussion of the relevant literature is interesting, unbiased, and highly informative.

The main criticism of the book is that, with such a detailed text, it is sometimes difficult to isolate the relevant facts and obtain a clear concept of the management of a particular disease. This problem could have been overcome by the use of tables of clinical signs and their management, and a summary at the end of each chapter.

There are one or two omissions or small criticisms. For instance in herpes simplex infection the text does not tell how to distinguish between active herpes simplex corneal ulceration and the breakdown of an inert ulcer to cause a recurrent erosion. The management of these two clinical conditions is entirely different. These, though, are minor points and do not detract from the overall excellence of the book. It is well written, highly informative, and should be on the shelves of all eye hospitals, libraries, available to anybody with an interest in ocular infection. It is highly recommended.

JAMES I. MCGILL

Basic Clinical Ophthalmology. By CALBERT I PHILLIPS. Pp. 256. £10.95. Pitman: London. 1984.

This paperback book is described as for the general practitioner and medical student and as an introduction to ophthalmology residents beginning in the specialty. Seventeen chapters by 12 different authors cover the topics of embryology and anatomy, clinical examination, squint, refractive errors, glaucoma, red eye, sudden loss of vision,

progressive loss of vision, neuro-ophthalmology, vascular retinopathies, trauma, eyelids, orbit, watering eye, tropical and hereditary ophthalmology, and preventive and social aspects.

There are many good black-and-white diagrams and photographs but unfortunately only a relatively small number of colour illustrations placed separately in the middle of the book. Colour illustrations are essential in any modern ophthalmology textbook to show the detail of clinical appearances matched with the text. *Basic Clinical Ophthalmology* has unfortunately fallen short here and will irritate the reader by making him refer constantly to another part of the book.

The detail provided is particularly good on clinical examination and glaucoma. In contrast the vascular and diabetic retinopathy chapter has 25 pages without a single adjacent illustration, and trauma has single separated illustrations of corneal abrasion and infected abrasion only, with no illustration of the vital-to-recognise penetrating eye injury. Preventive and social aspects are covered in a useful chapter properly emphasising practical aspects.

The modern undergraduate medical course has expanded significantly in recent years and the time available for ophthalmology, as with all specialties, is limited. The chapter on basic clinical ophthalmology is probably too detailed for most medical students but is well suited to the resident in ophthalmology in his first appointment. The uneven style of the book and the relatively few colour illustrations, separated from the text, divert the reader from a natural flow, which is probably as a result of the multiple authorship. For example, there is less than a page on the clinical presentation of senile cataract, with one illustration, but almost twice as much listing the rare and unusual causes of cataract such as galactosaemia and hypocalcaemia; detail concerning neutralising a spectacle lens, but not a mention in the whole book of colour vision!

In general it is a well laid out text, lacking in colour illustrations, but well suited to the new ophthalmology resident and at a reasonable price.

JAMES L KENNERLEY BANKES

Real Time Ophthalmic Ultrasonography and Biometry. By RICHARD S KOPLIN, MARTIN GERSTEN, BARTON HODES. Pp 187. US\$24.50. SLACK: New Jersey. 1985.

This well written spiral-bound handbook provides a sensible introduction to the clinician starting out in ophthalmic ultrasonography, covering topics such as 'three dimensional conceptualization,' and the 'indications and limitations of ultrasonic diagnosis.' Some useful diagnostic B scanning hints are to be found at the end of chapter 3. This book reflects the views of the Iowa and Cornell schools of ophthalmic ultrasound, and this has tended to make it particularly non-controversial.

The authors stress that 'ocular sonography is a dynamic process.' It should also be noted that, in differentiating certain lesions, they admit to adding historical information to the equation 'for the purposes of making a presumptive diagnosis.' Pathology of the eye is covered in chapters 9 to

14 and is followed by a chapter dedicated to a 'standardised' A scan technique. The use of A and B scan techniques in the diagnosis of intraocular and orbital tumours is covered in later chapters. Generally the B scan images are disappointing and some of the ultrasonic diagnoses rather fanciful—for example, the alleged demonstration of a choroidal rupture in chapter 14. The oft repeated principle that choroidal separation 'rarely extends posteriorly beyond the vortex vessels' does not accord with either the presented illustrations or the reviewers' experience. The book closes with a practical discussion on axial length measurement of the eye and calculation of lens implant power. References are to be found at the end of the book.

This is a lucid introduction for those intending to become involved in ophthalmic ultrasonography, though it offers no exceptional features in comparison with the several previously published books covering the same field.

MARIE RESTORI
DAVID MCLEOD

Échographie en Ophtalmologie. 2nd Edn. By J POUJOL. Pp. 79 F 139. Masson: Paris. 1984.

Written in French and soon to be translated into Italian, this book presents the possibilities and limitations of A scan and B scan ultrasonography in the author's experience; Dr Poujol performs nearly 3000 examinations a year. Some useful recommendations for B scan imaging are to be found at the end of chapter 2. Later chapters deal with biometry, methods of making echographic diagnoses, determining causes of error and artefacts, and ultrasonic examinations of the globe. It is refreshing that the author has considered that the ultrasonic appearances of surgical explants are important enough to be covered. Chapter 6 covers orbital examination by ultrasound. Some good images are to be found in this chapter; of particular note are the coronal sections. The book concludes with a page on the indications of ultrasonic examinations and the limitations of the techniques, with a brief look to the future. References are to be found at the back together with an alphabetical index.

This book will be of interest to those fluent in French. It contains some very interesting B scan images of various intraocular and orbital lesions.

MARIE RESTORI
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Notes

Cataract and implant meeting

The International Cataract, Implant, and Microsurgical Meeting will be held in Singapore on 29–31 May 1987. This is a joint meeting of the International Intraocular Implant Club and the Asia-Pacific Intraocular Lens Implant Association. This is a post-congress meeting of the 11th Asia-Pacific Academy of Ophthalmology Congress. Further information from Dr Arthur S M Lim, 3 Mt Elizabeth 0605–0608, Mt Elizabeth Medical Centre, Singapore 0922.

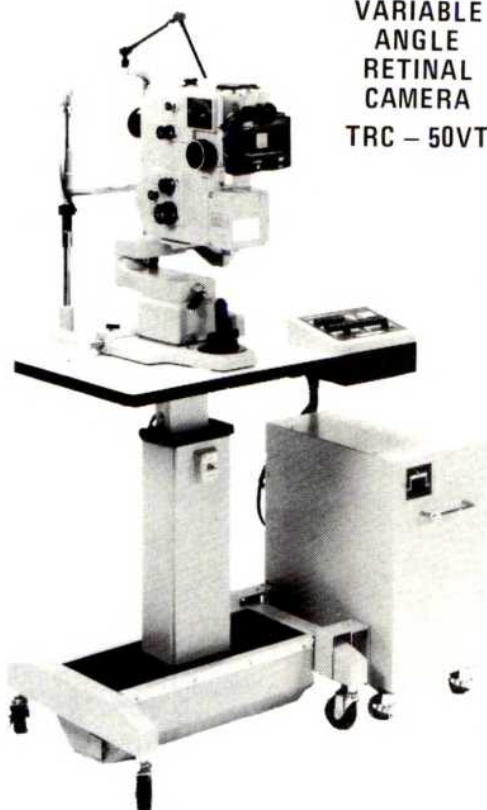
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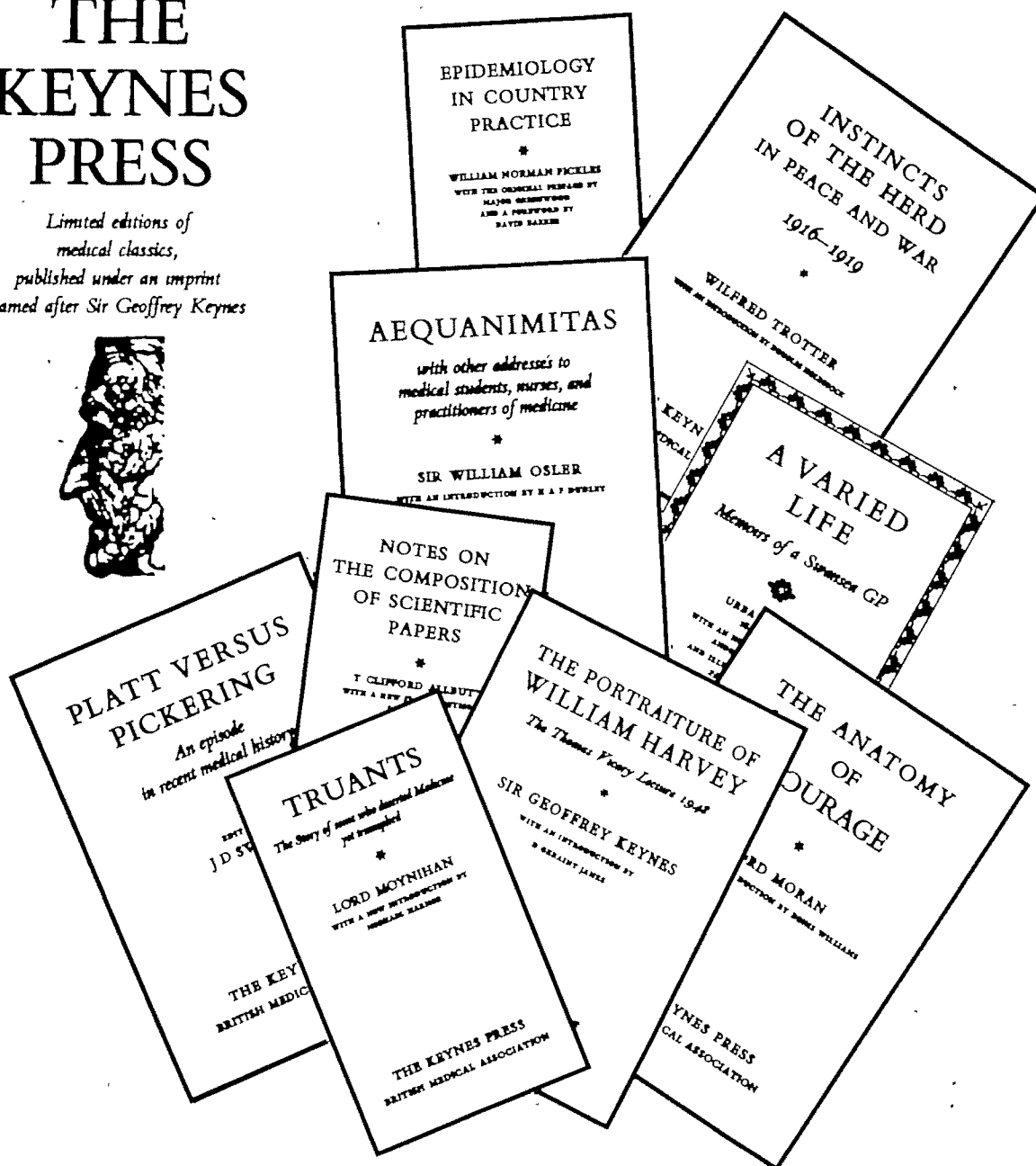
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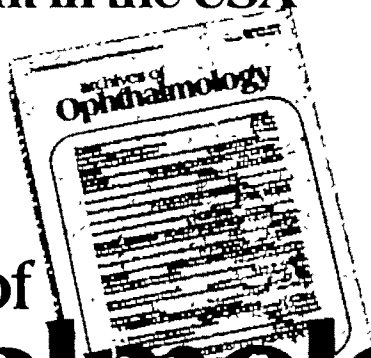
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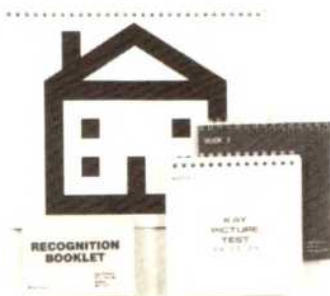
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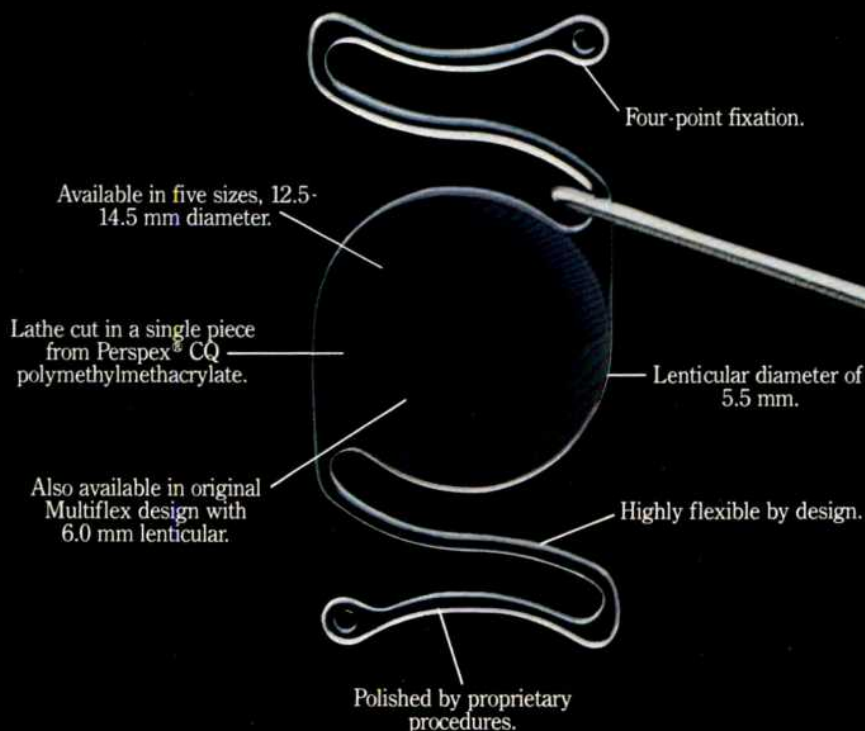
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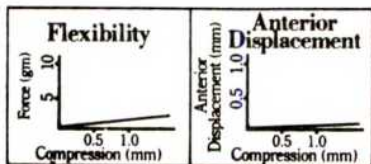
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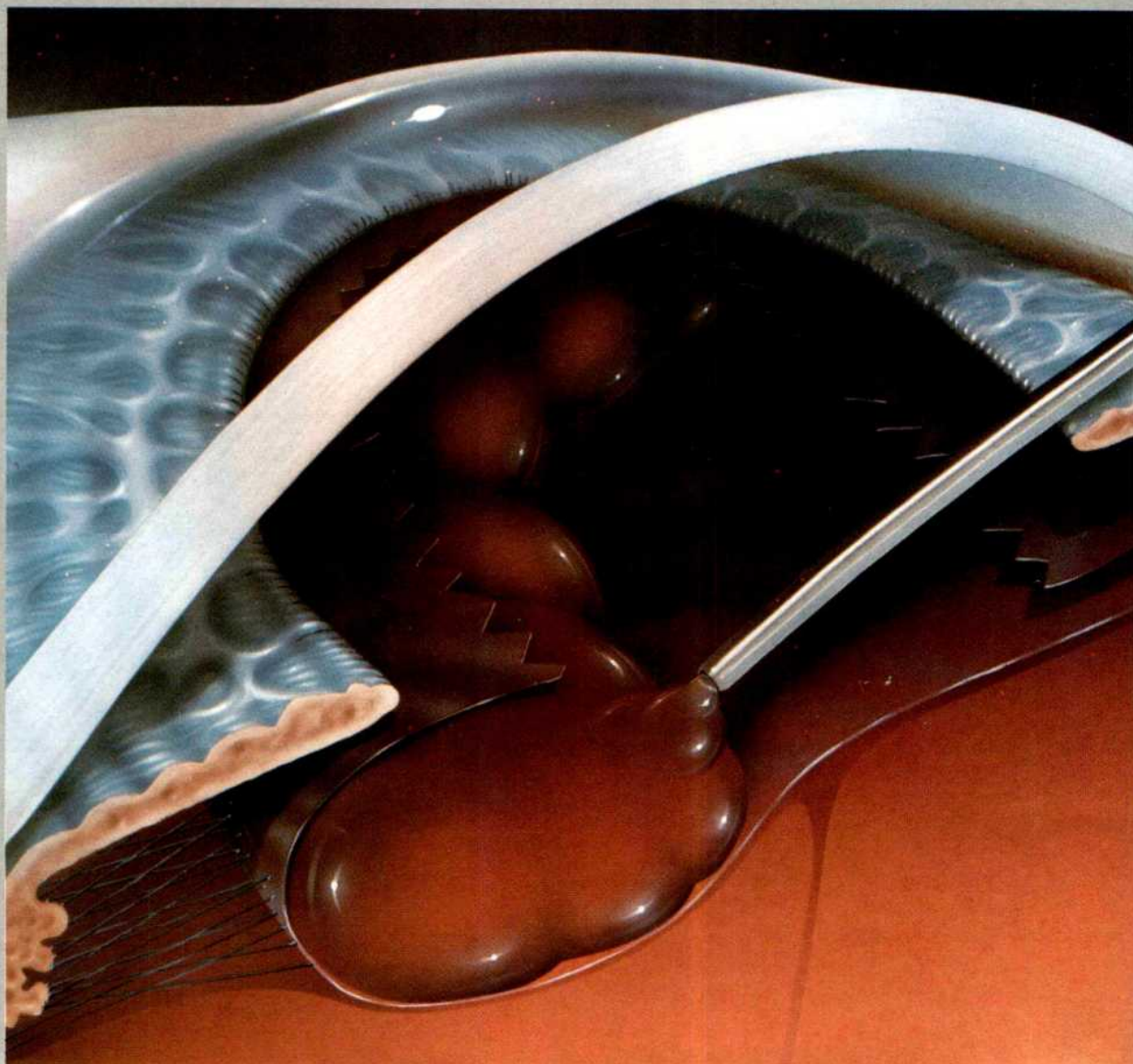
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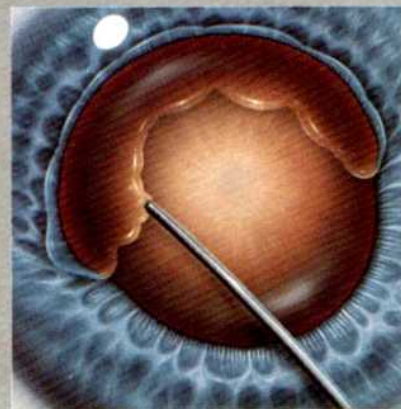


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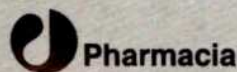
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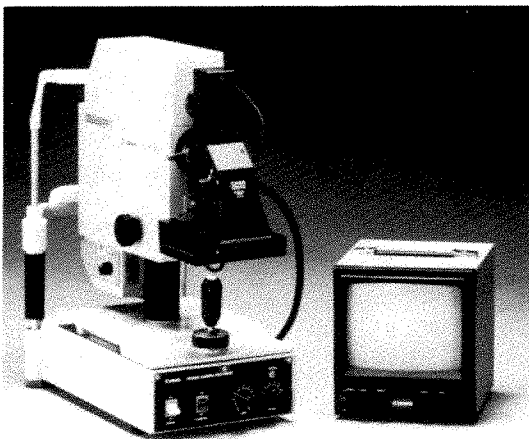
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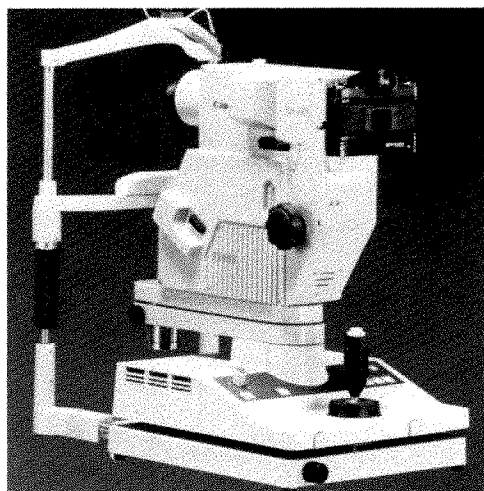
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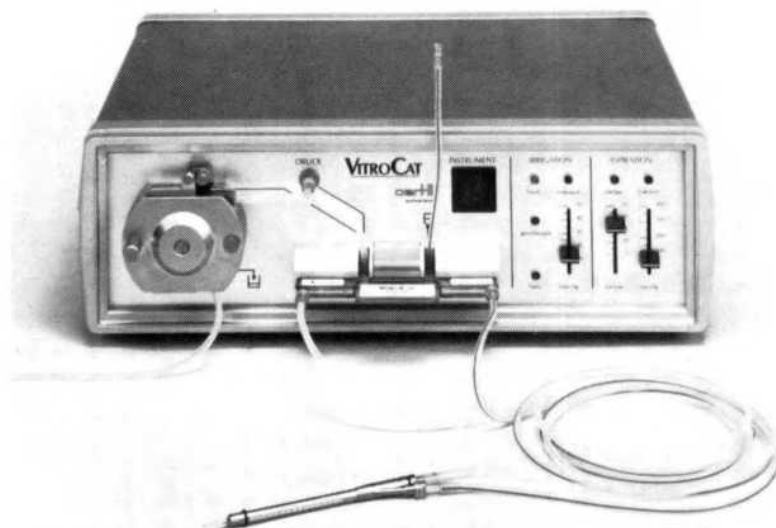
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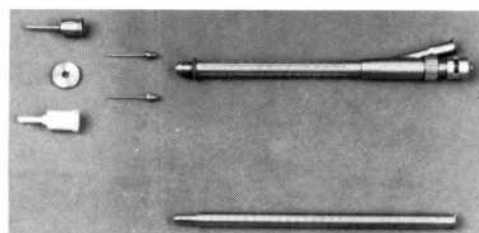


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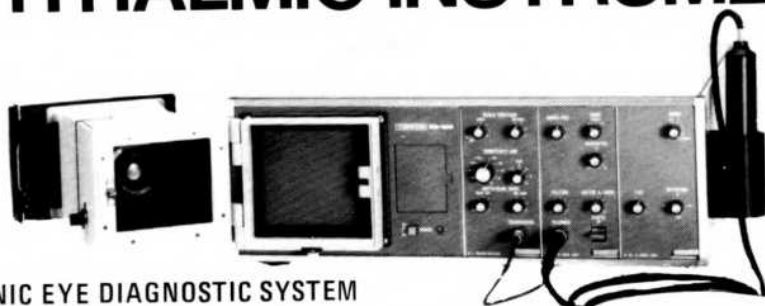
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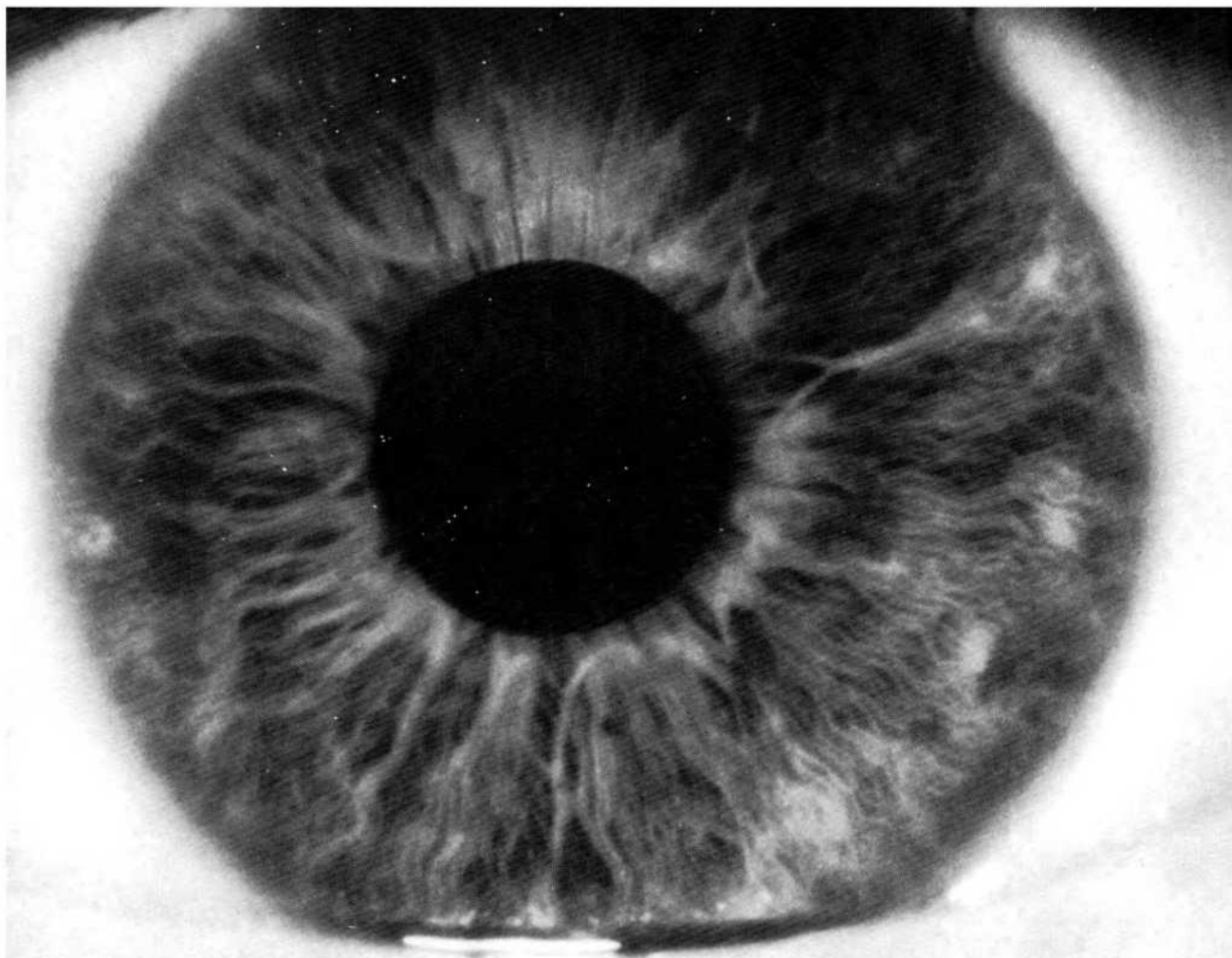
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Lacrimal streams: the demonstration of human lacrimal fluid secretion and the lacrimal ductules

A J BRON

From the Nuffield Laboratory of Ophthalmology, Walton Street, Oxford OX2 6AW

SUMMARY The clinical demonstration of the ductular orifices of the human lacrimal gland is reported. Lacrimal fluid secretion can be shown after instillation of 2% sodium fluorescein. Ductular orifices are visible on biomicroscopy. In keratoconjunctivitis sicca the lacrimal fluid streams appear normal, or to be diminished or absent.

The human lacrimal gland consists of a larger orbital portion which lies in a fossa on the frontal bone and a smaller palpebral portion which sits with its anterior border just above the lateral part of the upper fornix. Each portion is composed of lobules, and the secretions of the lobular acini pass first into fine interlobular ductules and finally into the definitive secretory ducts. The ducts of the orbital portion pass through and collect from the palpebral portion and enter the conjunctival sac in the superior fornix.¹ About 12 ducts open into the fornix, usually 4–5 mm above the upper border of the tarsal plate. Two to five ducts derive from the orbital lobe of the gland, and six to eight from the palpebral lobe. One or two are said to open in the region of the lateral commissure or even below this.^{2,3} It does not appear that the ductular orifices have been sought clinically, presumably because of the assumption that the openings would be too small to see. This contrasts with the situation in other species, where, for instance, in the rat or rabbit the orifice of the two secretory ducts of the exorbital lacrimal gland have been demonstrated under the microscope, and the ducts have been cannulated for the collection of pure lacrimal secretion.^{4,5}

The present paper stems from the chance observation in a patient with prominent palpebral lobes that the ductular orifices can be demonstrated in the presence of 2% fluorescein (Fig. 1). Dilution and fluorescence may be observed under a blue light, much in the manner of a Seidel test. Freshly secreted lacrimal fluid is seen streaming from each ductular orifice over the surface of the palpebral lobe.

In this preliminary paper the method of demonstrating lacrimal streams is presented, and the scope of the technique is discussed.

Material and methods

The patients are examined with the slit-lamp microscope using the blue exciting source.

The palpebral portion of the lacrimal gland may be prolapsed by asking the patient to look down and in, while the outer part of the upper lid is elevated by the observer's fingers and the lateral canthus is pulled temporally. The degree of prolapse varies widely.

A drop of 2% fluorescein is touched on to the exposed lacrimal gland to flood its surface. At the duct orifices the non-fluorescent lacrimal fluid dilutes the non-fluorescent 2% fluorescein to produce a dramatic dark stream whose margin is highly fluorescent (Figs. 2a, b).

Patients of both sexes attending the clinic or casualty department, their ages ranging from 11 to 84 years, were examined. A smaller group of patients with keratoconjunctivitis sicca was also examined. The number of duct orifices visible was counted and the fullness of tear flow crudely graded on a 0–4+ scale. The ease of prolapse of the palpebral lacrimal gland was also noted.

Results

In 31 patients without lacrimal gland disease, their ages ranging from 11–84 years (mean 58.7 years), 0 to 12 duct orifices were demonstrated at the surface of the prolapsed lacrimal gland with a mean of 4.48 (SD 2.9) on the right and 4.33 (SD 2.6) on the left.

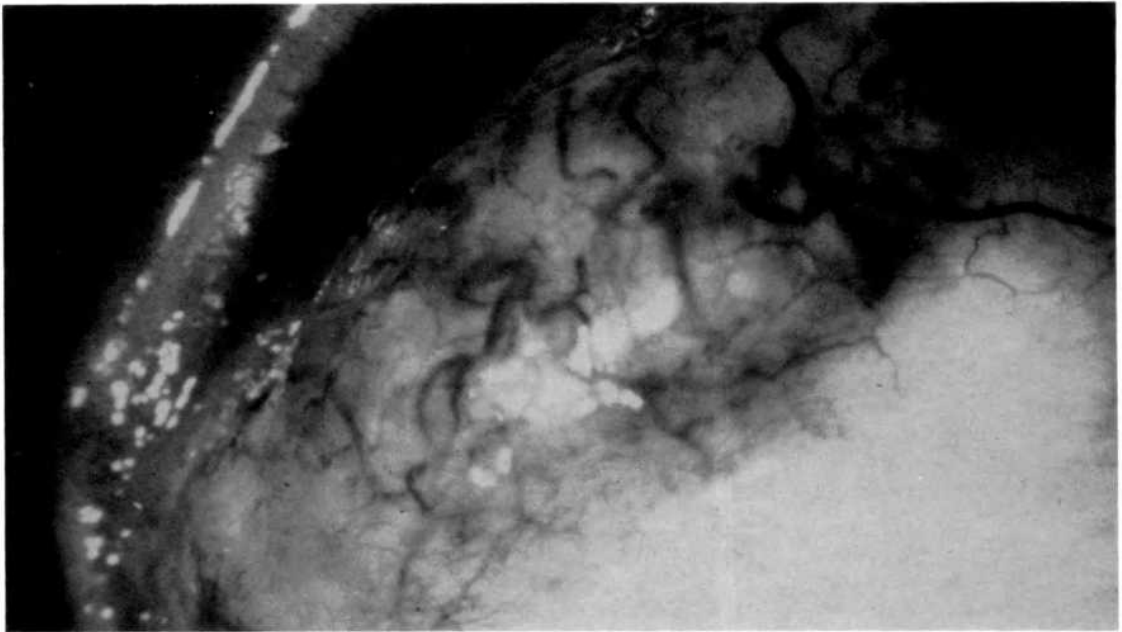


Fig. 1 Enlarged, prolapsed palpebral portion of the right lacrimal gland. Patient with suspected sarcoidosis.

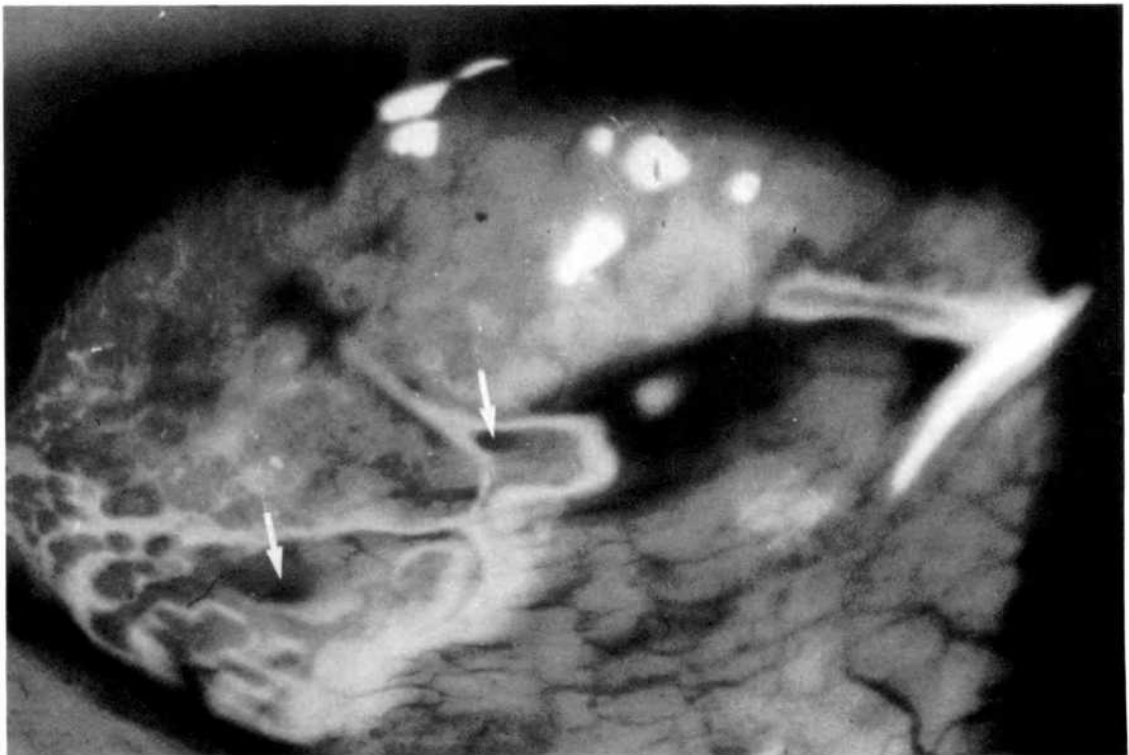


Fig. 2a Lacrimal fluid appearing at ductular orifices demonstrated with fluorescein. Normal gland.

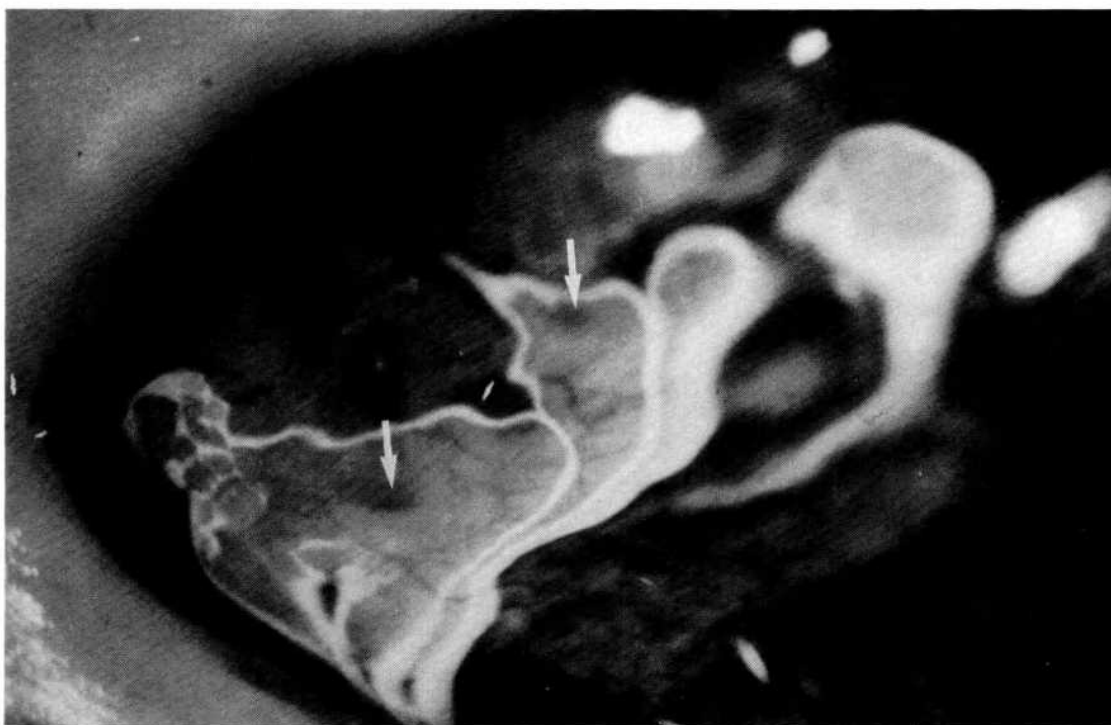


Fig. 2b Lacrimal streams showing 4+ flow rate; demonstrated with fluorescein. Same case as 2a. Orifices arrowed.

Because of the variable degree to which the lacrimal gland can be prolapsed in different subjects, this calculation undoubtedly underestimates the number of ducts presenting on the surface, and it was noted that the highest counts were achieved when prolapse of the gland (and therefore the overlying forniceal conjunctiva) was most complete, with 7 to 12 orifices presenting themselves. Nonetheless counts of 6 and below occurred over glands which appeared to prolapse readily, so that there may be a true variation in count between glands of different subjects. There was greater agreement in counts between the right and left glands, but this may in part have depended on similarity in gland prolapse between the two sides (Table 1).

The apparent rate of flow varied greatly from duct to duct. Often one duct secreted at a visibly greater rate than all the others and had a wider orifice. However, there were wide variations in apparent flow rates from individual glands without particular regard to the number of duct orifices counted; large orifices more commonly showed high flow rates. No attempt was made to equate apparent flow rates with the Schirmer test. To a small extent it was possible to modify the tear flow at some orifices by manipulating the lids and varying the degree of prolapse of

the gland. This applied particularly when flow was diminished.

When the palpebral lobe of the lacrimal gland was prolapsed and the associated upper fornix was everted, the gland had an elongated rounded or sometimes triangular profile. Duct orifices were not scattered randomly over its surface but followed the line of the upper fornix itself to form a more or less orderly row of openings extending to the canthus. The duct orifice at the canthus was the most constantly identifiable opening and lay in the conjunctiva immediately behind the canthus or within a millimetre of it. This 'sentinel' orifice was often a few millimetres away from the next orifice in the row, although at times two such orifices might lie close together.

Once a duct orifice had been identified with fluorescein it was often possible to observe the larger orifices in white light. Duct orifices might be round or slit-like, double contoured, exhibit a central aperture, or lie behind a short conjunctival fold. They were usually located in a less vascular zone than neighbouring conjunctiva.

Patients diagnosed as having keratoconjunctivitis sicca, or Sjögren's syndrome, on the basis of interpalpebral staining, reduced Schirmer's test results,

Table 1 *Assessment of lacrimal gland and lacrimal fluid flow in various subjects*

Age (years)	Sex	Ease of prolapse		Number of ductules		Sentinel ductule		Flow grade		Comment
		R	L	R	L	R	L	R	L	
71	F	2	2	6	8	+	+	4	4	L post op graft
23	M	2	2	7	5	+	+	4	4	Bilateral battery acid
20	F	2	2	3	3	+	+	4	3	R trauma
74	F	2	2	12	12	+	+	3	3	R implant
88	F	1	1	2	2	+	+	3	3	Normal
81	F	1	1	3	2	—	—	2	2	Chronic simple glaucoma
84	F	1	1	3	3	—	—	2	2	Normal
84	M	2	2	8	5	+	+	4	2	Normal
57	M	1	1	3	6	—	—	3	3	Normal
15	M	1	1	3	4	—	—	3	3	Normal
46	F	1	2	3	6	—	—	3	3	Normal
74	M	2	2	8	11	+	+	3	3	Normal
76	M	2	2	11	6	+	—	3	3	Normal
69	F	2	2	5	4	—	—	2	3	Normal
73	F	1	1	5	4	—	+	2	2	Normal
72	F	2	2	4	6	+	+	2	2	L scleritis
71	F	1	1	NA	2	NA	—	NA	3	Normal
46	M	1	1	NA	1	NA	—	NA	1	Normal
20	M	1	1	7	NA	+	NA	3	NA	R lithium burn
84	M	1	1	3	3	—	—	3	3	Normal
54	M	1	1	3	3	—	—	3	3	Normal
58	M	2	2	4	4	—	—	3	3	Normal
60	F	1	1	1	4	+	+	3	3	Normal
49	M	2	2	5	6	+	+	3	3	Normal
72	M	1	1	1	3	—	—	2	2	Normal
60	F	2	2	7	5	+	+	3	3	Normal
50	M	1	1	5	2	+	—	2	2	Normal
73	F	1	2	0	2	0	+	0	2	Normal
49	F	2	2	3	3	+	+	2	2	Normal
68	M	2	2	5	5	+	+	2	2	Normal
11	M	2	2	5	5	+	+	3	3	Normal
Mean 58.7				4.48	4.33					
SD				2.9	2.6					

NA=not assessed

and/or a reduced break up time, were examined by the test. In one patient with asymmetrical keratoconjunctivitis sicca and severe non-wetting features affecting the exposed and non-exposed conjunctiva

Table 2 *Lacrimal gland and lacrimal assessment in patients with keratoconjunctivitis sicca*

Age	Sex	Ease of prolapse		Number of ductules		Flow grade		Comment
72	M	1	1	2	2	2	2	KCS
69	F	2	2	6	6	3	3	KCS zero Schirmer
42	F	2	2	0	3	0	2	KCS punctate
43	F	2	2	4	4	2	2	KCS
52	M	2	2	2	2	0	0	Secondary Sjogren
37	F	2	2	3	2	2	1	Secondary Sjogren
68	M	1	2	1	2	2	2	KCS

KCS=keratoconjunctivitis sicca.

and cornea of one eye no lacrimal streams could be identified despite easy prolapse of the gland. The fellow lacrimal gland showed normal orifices, though only three were counted despite ready prolapse of the gland; flow was recorded as 2+. In another patient with disease of similar severity bilaterally a few orifices were identified on each gland, but no lacrimal flow. In other patients with keratoconjunctivitis sicca definite streaming was visible even in those with zero Schirmer's tests. However, apparent flow rates in such patients were no different from those observed in some normal subjects, with values graded 1-2+ (table 2).

Discussion

This appears to be the first demonstration of the visibility of the lacrimal ductular orifices in human

subjects. The demonstration of flow from individual orifices offers a series of fresh possibilities in the study of normal and abnormal lacrimal function. In this study a clinical grading of flow was made difficult by the presence of multiple streams of fluid for which it was difficult to generate a composite score. However, it may be feasible to collect the total lacrimal secretion in suitable subjects by 'capping' the prolapsed gland with a moulded cup attached to a collecting tube. The variable ability to prolapse the lacrimal gland means that the orifice count may not reflect the total number of ducts reaching the surface. However, when the gland prolapses fully, the counts will be reliable and will provide a precise number which can be compared between normal subjects and those with the sicca syndrome.

Many duct openings can be identified in white light even without prior demonstration with fluorescein, and it seems likely that the larger of these could be cannulated and the lacrimal fluid examined directly. It has already been possible to collect lacrimal fluid directly from the mouths of the lacrimal ductules. This will allow a determination of the origins of constituents present in tear fluid (which derives from the conjunctival secretions combined with the lacrimal fluid itself). This approach has already been developed experimentally in laboratory animals.^{4,5}

Apart from direct comparisons of electrolyte and protein constituents it will be possible to demonstrate whether mucus glycoprotein is secreted by the human lacrimal gland. At present such a proposition depends solely on the histochemical demonstration of sulphated and sialated glycoproteins within the lacrimal acini. This staining pattern is not specific to mucus glycoprotein^{6,7} and could reflect simply the presence of enzyme proteins.

It must be recognised that the manipulations necessary to expose the lacrimal gland surface in-

evitably stimulate reflex tearing, so that some comparisons between lacrimal fluid and tears will not be possible. On the other hand it may be feasible to examine more closely the effects of locally or parenterally administered secretagogues by this approach. Other approaches suggest themselves for consideration: comparison of steady state plasma and lacrimal fluid fluorescein levels after oral dosing with fluorescein will inform about the blood-barrier properties of human lacrimal gland; it may be possible to delineate lacrimal ductular structure by retrograde injection of radio-opaque dyes, much in the sense of sialography techniques but on a smaller scale. Finally, if it becomes possible to cannulate the lacrimal ductules, then certain pressing questions as to the role of the lacrimal gland in tear secretion can be answered.

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Biological variations of lysozyme concentration in the tear fluids of healthy persons

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SUMMARY Concentration of tear lysozyme was measured in healthy Indian subjects of the same racial group aged 2 to 78 years by a single radial immunodiffusion technique. Variations in its concentration between the two eyes, during the day, over a period of time, in both sexes, and in different age groups were studied. The diurnal and age-related changes in the concentration of tear lysozyme were found to vary to an appreciable extent. The mean lysozyme concentration in tears was lower in the morning and higher in the evening. It tended to be low in children under 16, rose and attained a plateau in the age group 16-45 years and fell in later life, though still remaining higher than in the children.

Lysozyme, discovered by Fleming,¹ is widely distributed in nature. It has been found in measurable quantity in tears, saliva, serum, nasal secretions, urine, neutrophils, and macrophages.² Since alteration in the lysozyme level in human tears has been observed in some ocular diseases,³⁻¹² its measurement can be of considerable diagnostic importance. However, an adequate knowledge of the biological variations is essential for valid comparisons of tear lysozyme levels between healthy and diseased subjects.

The present study was undertaken to find out differences, if any, in the tear lysozyme concentration between the two eyes and also the diurnal variation in the same eye. The concentrations of tear lysozyme over a period of time and in relation to age and sex have also been studied.

Material and methods

The study was carried out on healthy Indian subjects belonging to the same racial group. They were either volunteers or had attended the outpatient department of Guru Nanak Eye Centre, New Delhi, for refraction. They had no ocular or systemic disease. All of them had been in the uniform hospital environment for at least two hours prior to sampling.

In the first part of the study tear samples were

taken separately from each eye of 26 individuals at the same time to study any variation in the lysozyme level between the two eyes. In the second part of the study tear samples were obtained from the right eye in 18 individuals at four-hourly intervals from 6 am to 10 pm to determine diurnal changes while in the hospital environment. Tear samples (right eye, 10 am) from 22 individuals were taken on six different occasions (alternate months) to study variation with time during a period of one year. Finally, for age-sex related changes tear samples (right eye, 10 am) were obtained from 319 individuals (Table 1).

The tear samples were collected by a method described previously.¹³ The samples were stored at -20°C until assayed which was done within three to four days of collection. The level of tear lysozyme

Table 1 Distribution of tear lysozyme level in mg/ml in the two sexes in different age groups

Age in years	Males		Females		t	df	p
	No. of cases	Mean±SD	No. of cases	Mean±SD			
2-15	35	0.81±0.31	25	0.84±0.22	0.41	58	>0.60
16-30	50	1.68±0.66	37	1.65±0.70	0.20	85	>0.80
31-45	50	1.59±0.54	34	1.61±0.54	0.16	82	>0.80
46-60	37	1.30±0.37	26	1.19±0.33	1.19	61	>0.20
61-78	15	1.01±0.40	10	1.00±0.24	0.07	23	>0.90

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SI conversion mg/ml=g/l

was measured by a single radial immunodiffusion technique.¹⁴ Monospecific rabbit antihuman lysozyme serum and reference standard were obtained from Kallestad Laboratories, USA. A standard curve was constructed for each plate, and the concentration of tear lysozyme was determined with reference to the standard curve.

Results

The lysozyme level in tears in 26 individuals were: right eye: 1.31 ± 0.49 mg/ml and left eye: 1.27 ± 0.41 mg/ml. There was no statistically significant difference in the mean lysozyme level in tears between the two eyes ($t=0.81$ for 25 df, $p>0.40$). (SI conversion: mg/ml=g/l.)

The tear lysozyme level at different times of the day in 18 persons were: 6 am: 1.35 ± 0.42 mg/ml; 10 am: 1.44 ± 0.39 mg/ml; 2 pm: 1.41 ± 0.36 mg/ml; 6 pm: 1.47 ± 0.36 mg/ml; and 10 pm: 1.52 ± 0.32 mg/ml. Analysis of variance (Table 2) showed that there was a significant variation in the lysozyme level in tears during the course of the day ($F=4.32$ for 4 and 68 df, $p<0.01$). It was found that, when individual comparisons were made, the differences in the lysozyme concentrations in tears that attained statistical significance at the 5% level were those between the concentration at 6 am and that at 6 pm and between the concentration at 6 am and that at 10 pm.

The mean lysozyme levels in tears over a period of one year in 22 individuals were: January: 1.31 ± 0.46 mg/ml; March: 1.23 ± 0.36 mg/ml; May: 1.31 ± 0.33 mg/ml; July: 1.29 ± 0.33 mg/ml; September: 1.30 ± 0.29 mg/ml; and November: 1.21 ± 0.28 mg/ml. Analysis of variance showed that the variations were not statistically significant (Table 3). The mean

'between months' sum of squares was less than the mean 'within months' sum of squares. No formal test of significance was, therefore, found to be necessary.

The tear lysozyme levels in both sexes in the different age groups are given in Table 1. It was noted that differences between males and females were not statistically significant in any of the age groups. The data for the two sexes were therefore pooled for each group before making comparisons by age. The mean lysozyme levels in tears in various age groups are given in Table 1. The increase in the level of lysozyme in tears from the age group 2–15 years to 16–30 years was statistically significant ($p<0.001$). Again, the fall in the level of tear lysozyme from the age group 31–45 years to 46–60 years and from 46–60 years to 61–78 years was statistically significant ($p<0.001$).

Discussion

Valid comparisons of tear lysozyme level between healthy and diseased eyes are not possible without adequate control of biological variations. Several factors may influence the level of lysozyme in tears. A comprehensive study was therefore undertaken, and it showed that diurnal and age-related changes varied to an appreciable extent. There were no significant variations in the levels of tear lysozyme between the two eyes and at different times of the year.

Significant diurnal changes that we found in the level of tear lysozyme are interesting in that one earlier study¹⁵ showed no diurnal variation. No other study on diurnal variation is available for comparison. As regards variations in relation to sex, the present study is in agreement with the work of other investigators who found the level of tear lysozyme to be independent of sex.^{8, 10, 15, 16}

There are several reports on age-related changes in the level of tear lysozyme which are conflicting.^{8, 10, 17, 18} Some investigators have found that there is no effect of age on the tear lysozyme levels.^{8, 10, 16, 17, 19} Bonavida and Sapse²⁰ found lower levels of tear lysozyme at the upper and lower extremes of age. Pietsch and Pearlman¹⁵ observed that the level of lysozyme in tears fell continuously after the age of 10 years. Mukai⁹ found that in healthy subjects tear lysozyme reached peak levels in the age group 11 to 20 years and tended to decrease thereafter. Mackie and Seal²¹ also noted a gradual decline of tear lysozyme levels with advancing age. Morsky and Aine²² found a tendency to declining concentrations after 31–45 years of age. McGill *et al.*¹⁸ found that tear lysozyme levels started falling after the age of 40 years at a rate of 1 mg/dl (10 mg/l) per year of age. Our study on a large number of subjects shows that the level of tear lysozyme tends to be low in the

Table 2 Variation in tear lysozyme concentration during the day: analysis of variance

Source of variation	df	Total sum of squares	Mean sum of squares	F
Between periods	4	34.27	8.57	4.32
Between individuals	17	1068.90	62.88	31.76
Error	68	134.93	1.98	
Total	89	1238.10	—	—

Table 3 Variation in concentration of lysozyme in tears over a period of time: analysis of variance

Source of variation	df	Total sum of squares	Mean sum of squares
Between months	5	0.26	0.05
Within months	126	63.88	0.51
Total	131	64.14	—

younger age group (2–15 years: 0.82 mg/ml), rises and attains a plateau in the age group 16–45 years (16–30 years: 1.67 mg/ml; 31–45 years: 1.60 mg/ml), and then falls significantly in later life (46–60 years: 1.26 mg/ml; 61–78 years: 1.01 mg/ml) but still remains higher than that found in younger people. The earlier studies, where no alterations of tear lysozyme level with age were detected, were small and the methods used in them were less sensitive.

Our findings suggest that in studying the lysozyme levels in the tears of diseased people it is necessary to select separate controls matched for age from among healthy people for each disease group, and to collect all the tear samples at a particular time of the day, for valid comparisons to be made.

The statistical analysis was done by Mr G P Mathur, statistician, New Delhi Tuberculosis Centre, New Delhi

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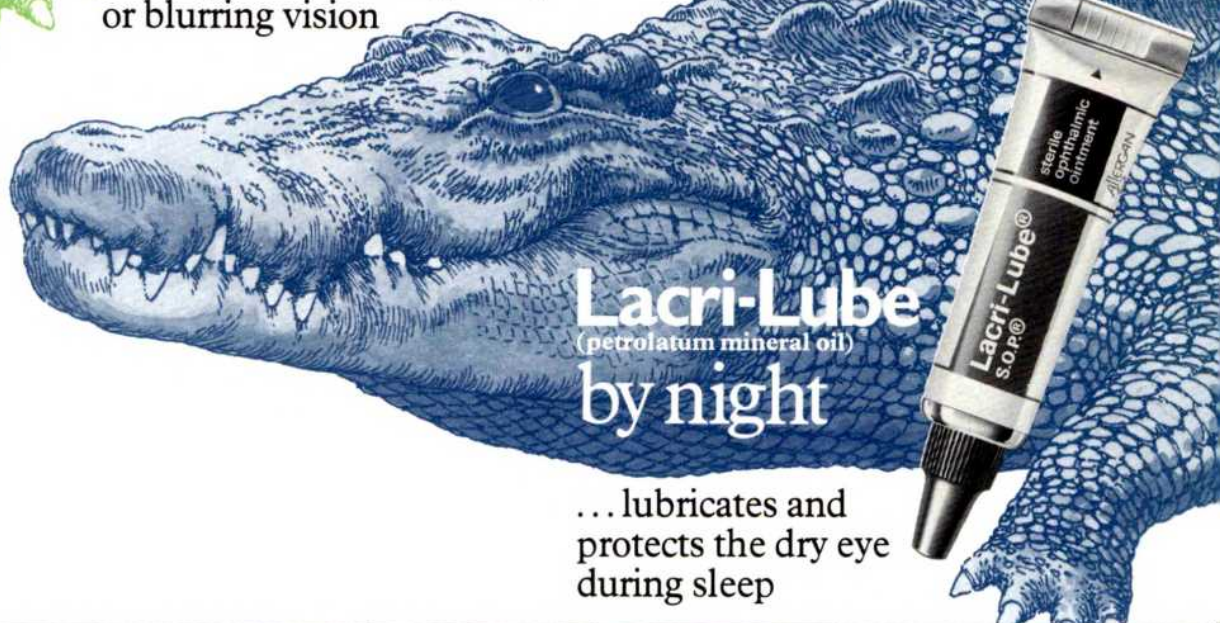
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'Timoptol' may cause side effects of systemic beta-blockade. Cardiac

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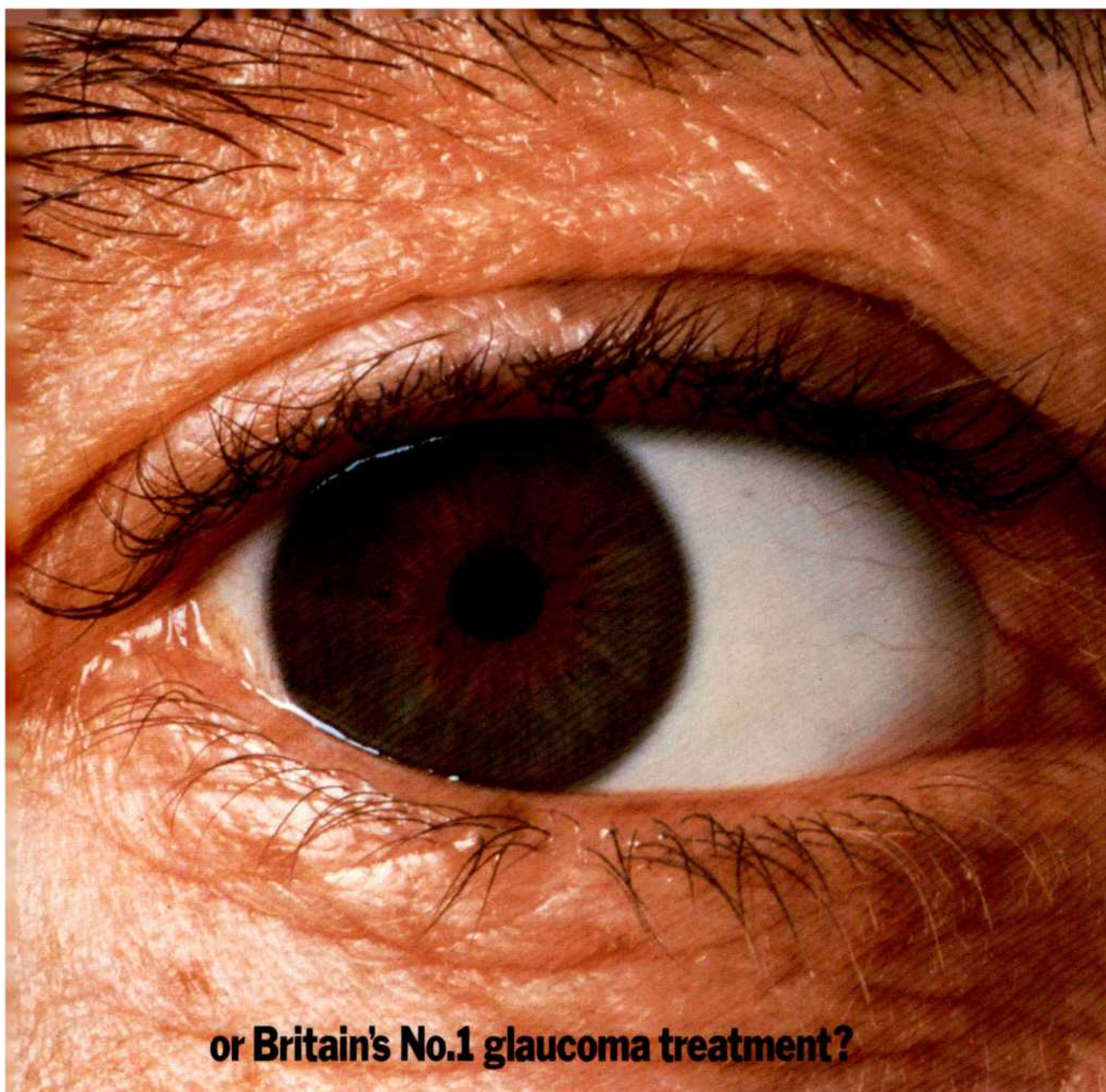
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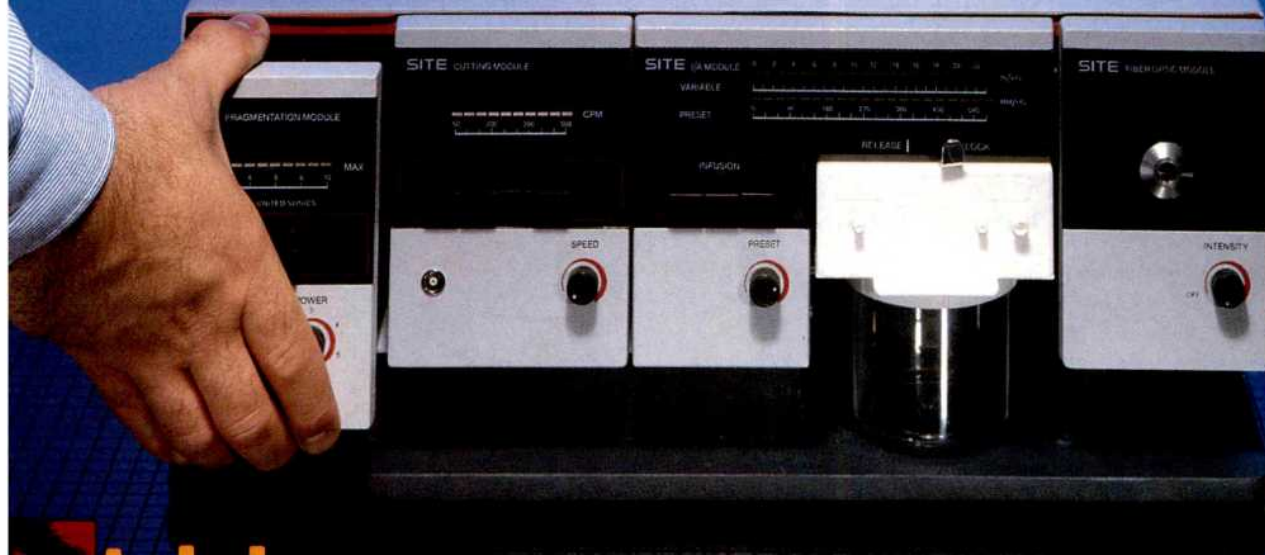
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Does unidirectional vesicular transport occur in retinal vessels?

T A GARDINER AND D B ARCHER

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SUMMARY This paper challenges the hypothesis that the smooth 80 nm plasmalemmal caveolae found in abundance at the abluminal aspect of the endothelium in retinal blood vessels participate in a unidirectional vesicular transport mechanism. Evidence is presented which indicates that horseradish peroxidase, when introduced to the extracellular space of the retina via the vitreous body, may enter the intravascular compartment through junctional incompetence which occurs at or after enucleation of the eye. It is proposed that the plasmalemmal caveolae at the abluminal plasma membrane of endothelial cells in retinal blood vessels are static structures which facilitate the transport of small solutes and ions across the blood retinal barrier.

An unusual polarity has been described in the plasmalemmal caveolae in the vascular endothelial cells of the brain^{1,2} and retina.^{3,4} Caveolae are present in large numbers at the abluminal plasma membrane yet are relatively sparse at the luminal cell surface. The filling of such caveolae with intravitreal horseradish

peroxidase (HRP) together with a simultaneous occurrence of the tracer in the lumina of the same vessels led the authors of a recent study⁴ to conclude that 'unidirectional vesicular transport' occurs in retinal blood vessels, that is, from the extracellular space to the intravascular compartment. Nevertheless, 'in transit' vesicles were not demonstrated, and no corresponding complement of plasmalemmal caveolae were identified at the luminal plasma membrane.

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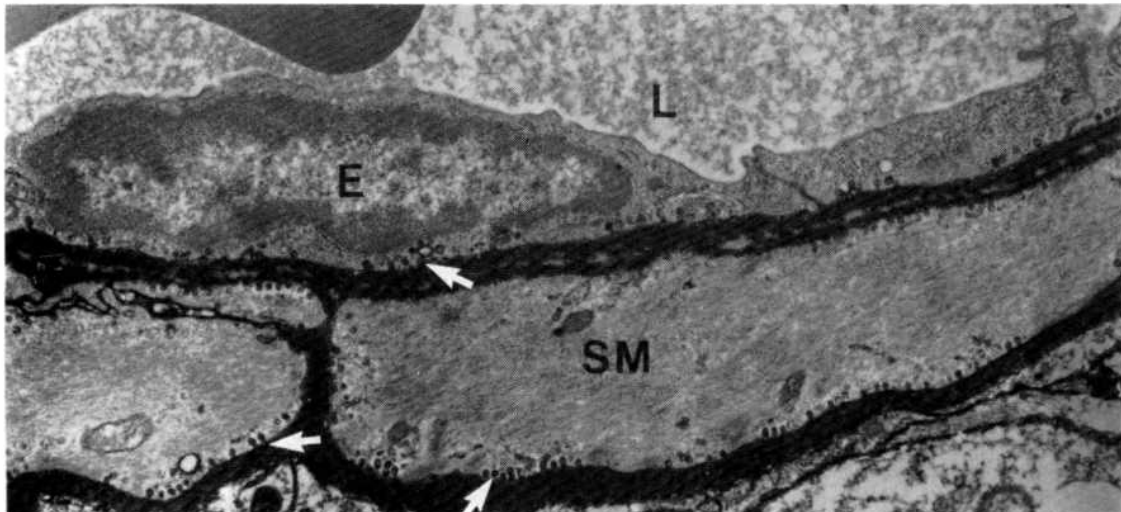


Fig. 1 Retinal artery (rat): intravitreal horseradish peroxidase (immersion fixation). Peroxidase reaction product fills the basement membranes of a retinal artery. The sarcolemmal caveolae of the smooth muscle cells (SM) and the abluminal plasmalemmal caveolae of the endothelium (E) are outlined by the tracer (arrows). Lumen (L). ($\times 12\,000$).

Westergaard and Brightman¹ suggested that the abluminal plasmalemmal caveolae of cerebral vessels were static structures. This view was confirmed by Broadwell *et al.*,² who found that the abluminal caveolae of endothelial cells in the cerebral vessels of the mouse did not transport intraventricular horseradish peroxidase even after 24 hours' exposure to the tracer. Accordingly, this study was undertaken to elucidate the function of the plasmalemmal caveolae at the abluminal surface of the retinal vascular endothelium.

Materials and methods

Three male Wistar albino rats were anaesthetised by intraperitoneal injection of sodium pentobarbital. Horseradish peroxidase (Sigma type VI) dissolved in Hams F10 tissue culture medium (10 mg HRP/ml) was injected into the vitreous body of both eyes in each animal. 50 μ l of peroxidase solution was injected into the vitreous body via the peripheral retina. After 30 min the eyes were enucleated and fixed by immersion in 2.5% glutaraldehyde in 0.1 M cacodylate buffer. Areas of retina remote from the injection site were selected for horseradish peroxidase demonstration and processed as previously described.⁵

Results

Thirty minutes after intravitreal injection of horseradish peroxidase its reaction product was found

throughout the entire extracellular space of the retina. The tracer had penetrated the basement membranes of both large and small blood vessels (Figs. 1 and 2) and filled the abluminal plasmalemmal caveolae of the endothelial cells. The caveolae usually occurred as single units, although composite structures were often seen (Fig. 3). Labelled vesicular images were seen adjacent to the abluminal plasma membranes of the endothelial cells, but no 'in transit' vesicles were found in either the central or apical cytoplasm (Fig. 3). At the time of examination (30 min postintravitreal injection of HRP) the multivesicular bodies of the endothelial cells showed no evidence of peroxidase incorporation (Fig. 3). The sarcolemmal caveolae of vascular smooth muscle cells (Figs. 1 and 3) filled uniformly with peroxidase, though there was no evidence of tracer internalisation. A large proportion of the vessels showed HRP reaction product within the fixed plasma in the vessel lumen.

The intercellular clefts bounded by the tight junctions of the endothelial cells were usually free of peroxidase (Fig. 3). However, it was possible to find vessels where the tight junctions had been breached and where peroxidase was present throughout the intercellular clefts (Fig. 4) and in the vessel lumen (Figs. 2, 4, and 5). 'Tight' and 'leaky' junctions could be found in the same vascular profile (Fig. 6). However, the observed sites of junctional incompetence were discrete, and even in these regions the adjacent plasma membranes showed no gross separation (Fig. 4).



Fig. 2 Retinal capillary (rat): intravitreal horseradish peroxidase. Peroxidase reaction product fills the vascular basement membranes and outlines numerous abluminal plasmalemmal caveolae (white arrows) in the endothelium (E). The plasma in the vessel lumen is also stained by peroxidase reaction product. Lumen (L). ($\times 15\ 000$).

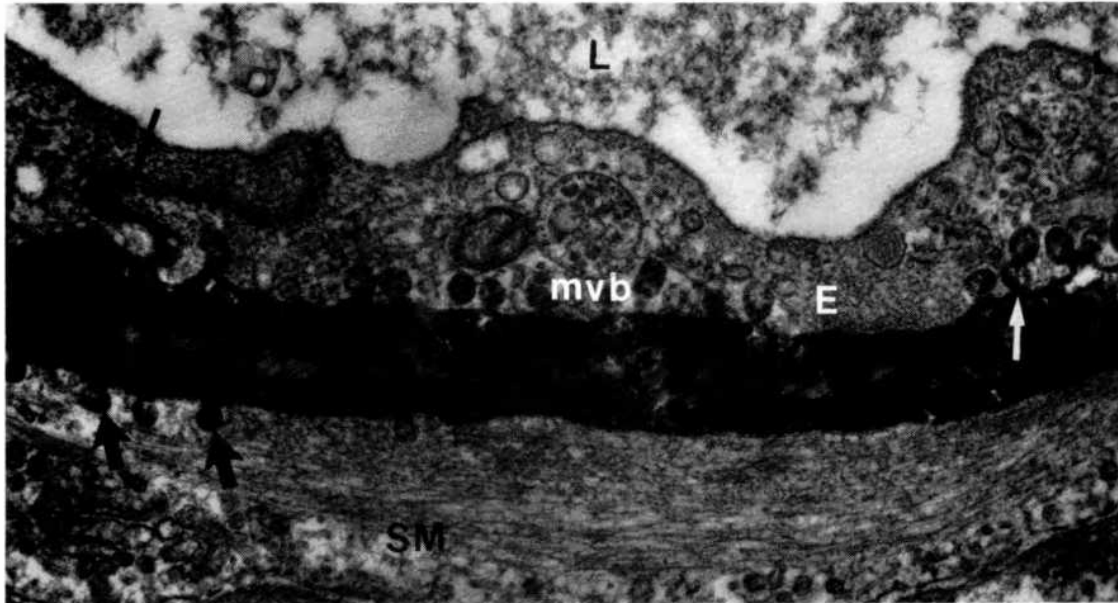


Fig. 3 Retinal artery (rat): intravitreal horseradish peroxidase, immersion fixation. Bilobular vesicular structures associated with the abluminal plasma membrane of endothelial cell (E) are filled by peroxidase reaction product (white arrow), but a nearby multivesicular body (mvb) shows no evidence of tracer ingestion. Tracer does not penetrate beyond the first tight zone of the junctional complex (thin black arrow). The sarcolemmal caveolae (thick black arrows) of a smooth muscle cell (SM) are stained with peroxidase reaction product. Lumen (L). ($\times 45\,500$).

Discussion

The preponderance of abluminal over luminal plasmalemmal caveolae in the endothelia of cerebral vessels was first recorded by Westergaard and Brightman,¹ and a similar situation has recently been described in retinal vessels.^{3,4} To test the possibility that such caveolae play a role in macromolecular transport from the extracellular space of the retina to the intravascular compartment they were presented

with a traceable protein (horseradish peroxidase) via the vitreous body. Peyman *et al.*⁶ noted that intravitreal horseradish peroxidase fully penetrated the rabbit retina within 15 minutes. Accordingly we considered that 30 minutes was an adequate time for intravitreal horseradish peroxidase to penetrate to the blood vessels of the thinner rat retina and permit possible endocytosis at the abluminal surface of the endothelium. In none of the retinal vessels examined was there evidence of vesicular transport or internali-

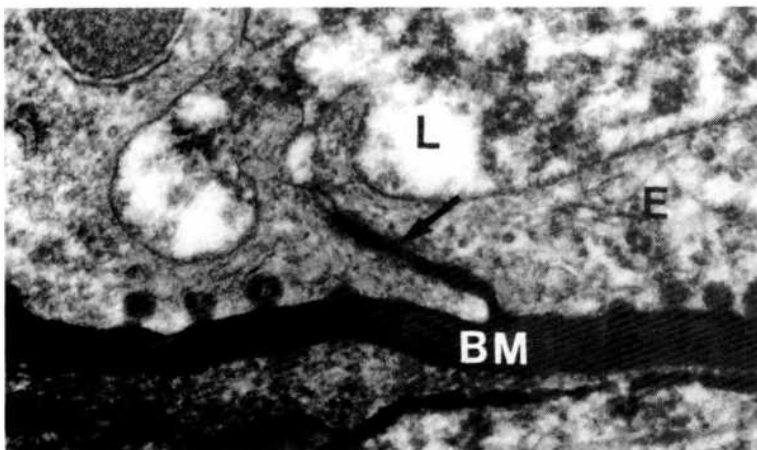


Fig. 4 Retinal capillary (rat): intravitreal horseradish peroxidase. Peroxidase has passed through the cell junctions in this vessel (arrow) and is present in the lumen (L). Endothelial cell (E). Basement membrane (BM). ($\times 50\,000$).

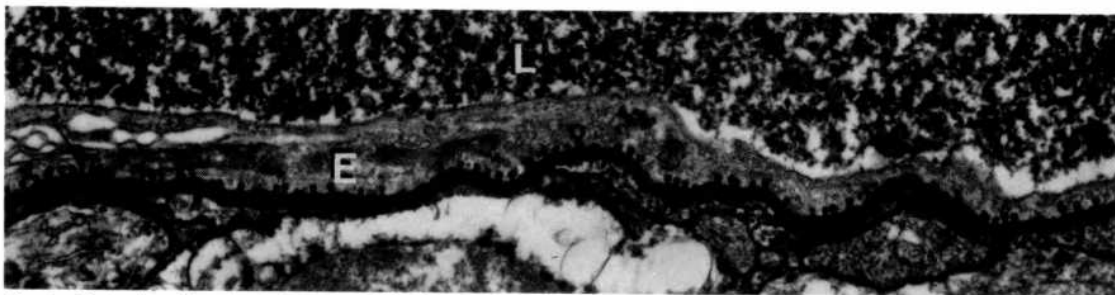


Fig. 5 Retinal capillary (rat): intravitreal horseradish peroxidase. Peroxidase reaction product stains the basement membrane and abluminal plasmalemmal caveolae of the endothelium (E). Tracer is present in the lumen (L). ($\times 15\,000$).

sation of peroxidase by the abluminal plasma membranes of the endothelial cells. If transcellular vesicular transport had been in progress at the time of fixation, it is almost certain that a few labelled vesicles would have been seen either 'in transit' or at the luminal plasma membrane. These results support the suggestion of Westergaard and Brightman,¹ who considered that the abluminal plasmalemmal caveolae of cerebral vessels were static structures involved more with ion fluxes than macromolecular transport.

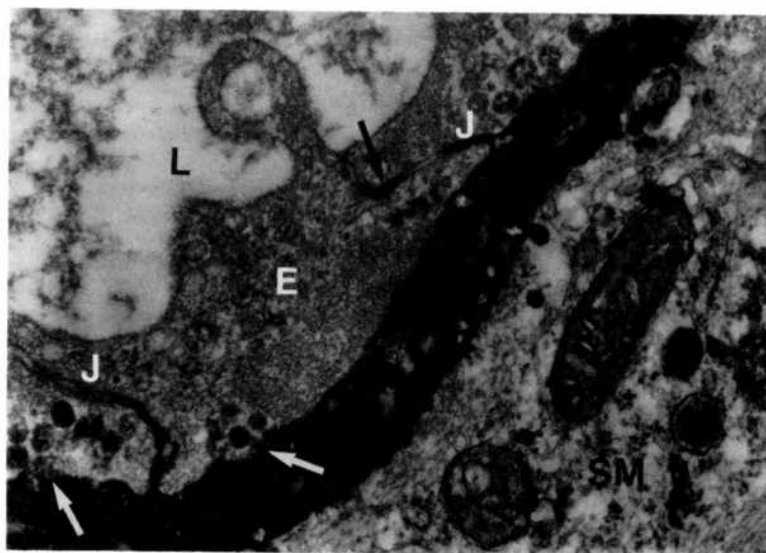
Ultrathin serial sectioning of frog mesenteric capillaries⁷ and rat heart capillaries⁸ has revealed that the plasmalemmal caveolae of vascular endothelial cells often form racemose invaginations deep into the endothelial cell cytoplasm. Conventional thin sections give the false impression that such structures are free in the cytoplasm while in reality they are still connected to the cell surface. In the present study the abluminal caveolae did not appear to form particularly deep invaginations, as 'vesicle' images were

never encountered at a depth at which direct communication with the cell surface was not a likely possibility.

The presence of numerous abluminal caveolae in the endothelium of cerebral vessels and the danger of misrepresenting them as transport vesicles was highlighted by Broadwell *et al.*² These workers found no evidence of vesicular transport of intraventricular horseradish peroxidase even after 24 hours' exposure to the tracer.

The results of the present study are contrary to those of a recent report by Raviola and Butler,⁴ who described a 'unidirectional vesicular transport mechanism in retinal vessels' based on observations of intravitreally administered horseradish peroxidase within the retina. The authors observed HRP reaction product staining the fixed plasma within the lumina of the retinal vessels and attributed it to the activity of a vesicular transport mechanism arising from the abluminal plasmalemmal caveolae. The authors contended that the absence of a correspond-

Fig. 6 Retinal arteriole (rat): intravitreal horseradish peroxidase. Two junctional complexes (J) are present at the lateral aspects of a single endothelial cell (E). The tight junction at one end of this cell has leaked at a point outside the plane of section and admitted peroxidase to the intercellular cleft (arrow). In regions where the abluminal plasmalemma is obliquely sectioned the associated caveolae appear as 'vesicles' (white arrows). Lumen (L), Smooth muscle cell (SM). ($\times 40\,000$).



ing number of plasmalemmal vesicles at or even approaching the luminal surface of the endothelium did not 'seem to represent a cogent objection' to the notion that the abluminal plasmalemmal caveolae give rise to transport vesicles. We suggest that the failure to demonstrate a progression of labelled vesicles or vesicle derived structures across the endothelium presents a major difficulty to the hypothesis that vesicular transport occurs in these vessels. Raviola and Butler did publish an electron micrograph of two peroxidase labelled caveolae which were thought to be discharging their contents at the luminal surface of the endothelium. However, they did not mention that peroxidase arriving in the vessel lumen by whatever route is likely to stain the luminal glycocalyx of the endothelium, including that on the interior of the plasmalemmal caveolae.⁹ The glycocalyx or anionic surface coat is present around most cells,¹⁰ and its presence is well recognised in vascular endothelia.¹¹ Sigma type II HRP as used by Raviola and Butler is known to be a mixture of several different isoenzymes, some of which are cationic and as such have an affinity for the polyanions of the glycocalyx. Their published micrograph clearly shows positive staining by adsorbed peroxidase within the glycocalyx of the luminal plasma membrane which is continuous with the caveolae said to be 'discharging'. Furthermore, the peroxidase stained layer within the caveolae is clearly identical to that on the plasmalemma proper. The tracer which was present in the vessel lumen in the study by Raviola and Butler and in the present investigation was obviously the result of a post-mortem phenomenon, as immersion fixation was used in both cases. Accordingly the 'unidirectional vesicular transport' hypothesis presented by Raviola and Butler as a physiological mechanism seems unlikely.

The present study has shown that the 'tightness' of the endothelial cell junctions in the retinal vessels may be functional, that is, be dependent on a normal relationship between intravascular and tissue pressure. The fall in intravascular pressure at enucleation (when the central retinal artery and vein were severed) may have allowed the relatively high tissue pressure to force peroxidase laden fluid from the extracellular space through the cell junctions and into the vessel lumen. As soon as the central retinal artery and vein are severed, any pressure applied to the globe in subsequent handling will tend to transfer fluid from the extracellular space of the retina to the intravascular compartment. It is therefore suggested that in experiments of this type the intraocular pressure should be reduced to zero before interrupting the retinal blood supply.

Preliminary experiments on monkeys in this laboratory suggest that intravitreal peroxidase is not

found in the intravascular compartment if the intraocular pressure is reduced before cutting the optic nerve. Although Raviola and Butler illustrated an intact cell junction in a vessel showing peroxidase in the lumen, the present study has shown that competent and incompetent junctions may be present in the same vessel. Therefore it does not appear to be necessary for all or even a large proportion of the cell junctions within the retinal vessels to leak in order to fill considerable segments of the vascular bed with peroxidase laden fluid. Furthermore, as the trans-junctional 'leaks' observed in the present study were subtle and not noticed at all by Raviola and Butler in their study, it seems that a relatively small number of incompetent vessels may have been responsible for the presence of intravascular peroxidase. It is therefore not surprising that attempts to arrest the transport of HRP from the extracellular space to the vessel lumen by cooling the eye and using metabolic poisons should have failed in the study by Raviola and Butler.

If the abluminal plasmalemmal caveolae are not concerned with the transport of macromolecules, then it remains to be determined just what their precise functions are. In a general sense it seems likely that their role may be analogous to those of the sarcolemmal caveolae of smooth muscle cells,¹²⁻¹⁴ which greatly increase the surface area of the plasma membrane for more subtle membrane functions—for example, simple or facilitated diffusion or active transport. Caveolae would provide a stable micro-environment conducive to the operation of specific transport systems within the turbulent environment of the vascular wall. It is relevant that enzyme systems associated with active transport have been demonstrated within endothelial plasmalemmal caveolae.^{15,16} Furthermore the membrane associated ATPase activity of retinal¹⁷ and cerebral¹⁸ vascular endothelia shows a distinct polarity, being located at the abluminal surface. Cunha-Vaz and Maurice¹⁹ have demonstrated the ability of the retinal blood vessels to pump organic anions out of the retina against a concentration gradient. We suggest that this 'pump' and perhaps other specific extrusion systems for metabolic wastes are likely to be located at the abluminal plasma membrane of the retinal endothelial cells and that the abluminal plasmalemmal caveolae represent the structural facility required to accommodate such systems.

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Acute posterior multifocal placoid pigment epitheliopathy associated with diffuse retinal vasculitis and late haemorrhagic macular detachment

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SUMMARY A 20-year-old healthy man suffered rapid loss of bilateral central vision with placoid lesions at the level of the retinal pigment epithelium and choriocapillaris scattered in the posterior pole of the fundus. In addition, acute vasculitis of the retinal veins was remarkable and widespread throughout the posterior pole and midperiphery. These inflammatory signs subsided in several weeks and were succeeded by recovery of the normal visual acuity with residual pigment derangements in the deep retina. Sixteen months after the onset of the disease choroidal neovascular membranes developed in the macular region of the left eye, followed by haemorrhagic macular detachment and marked visual loss. Significant increases in the serum cold agglutinin titre occurred as isolated laboratory findings concurrently with the acute stage of the disease and the late macular complication, though no clinical or other laboratory sign suggested viral infection.

Acute posterior multifocal placoid pigment epitheliopathy, originally defined by Gass,¹ is a disease characterised by the acute onset of multiple, yellow or cream-coloured, placoid lesions at the level of the retinal pigment epithelium and choriocapillaris scattered in the posterior pole of the fundus. The disease affects both eyes of healthy young adults with or without a history of recent viral illness involving the upper respiratory or gastrointestinal tract just prior to the onset of visual symptoms, and it leads to a rapid loss of central vision when the macular region is involved. The prognosis is favourable, so that the characteristic lesions resolve over several weeks, leaving alternating depigmentation and pigment clumping, with remarkable improvement of visual function.¹⁻⁹ Occasional abnormalities associated with the acute stage of the disease include episcleritis,^{4,9} subconjunctival haemorrhage,⁹ anterior uveitis^{4,5,8,10} or vitreitis,^{8,10,11} serous detachment of the sensory retina,^{2,6,9,10,11} optic disc swelling,^{3,9,11,12} segmental retinal vasculitis,^{9,12} and small retinal haemorrhages.^{4,10,12}

We describe a case of acute posterior multifocal placoid pigment epitheliopathy which, in addition to the typical clinical picture, had diffuse inflammatory reactions of the retinal veins in the acute stage of the disease and, more than a year after complete subsidence of the inflammation with recovery of the normal visual acuity, developed haemorrhagic macular detachment due to choroidal neovascularisation, leading to irreversible visual loss. Another noticeable finding in this case was raised titres of serum cold agglutinins as an isolated laboratory abnormality.

Case report

A 20-year-old healthy Japanese man developed central blurred vision of both eyes four days prior to his initial visit to us. He had no antecedent general illness. On examination his best corrected visual acuity was 0.3 in the right eye and 0.4 in the left eye. Tests of motility, the pupils, applanation tonometry, external and anterior segments, and media gave normal results in both eyes. Ophthalmoscopic examination of the right fundus revealed multiple, generally round and occasionally confluent, whitish-yellow

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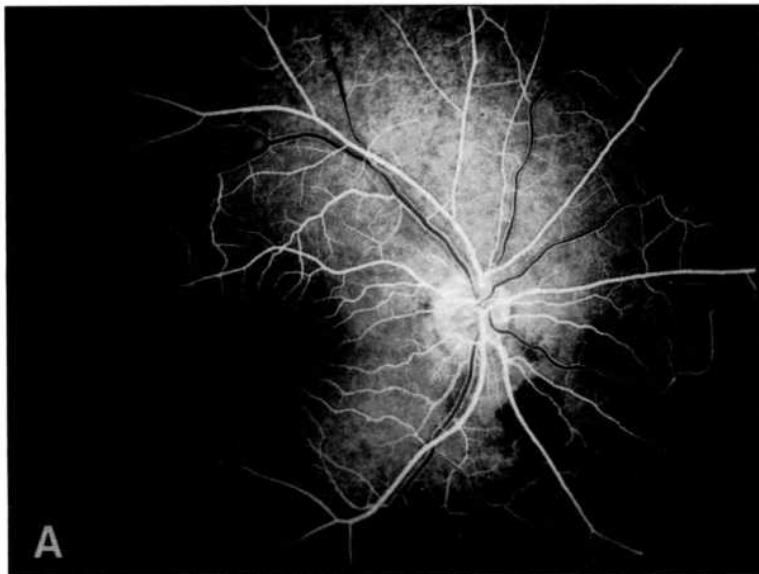
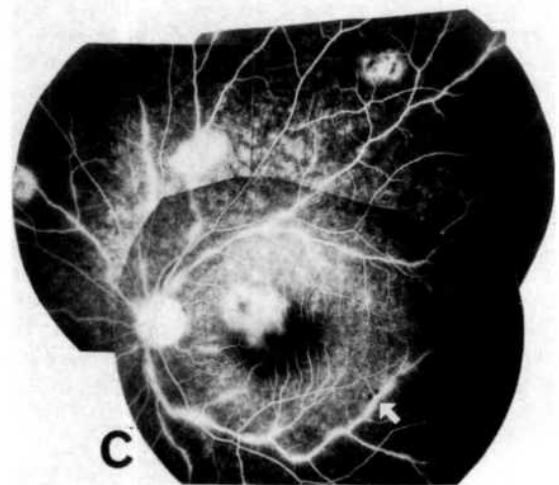


Fig. 1 Fluorescein angiograms recorded one week after the onset of disease. (A) Early phase of the angiogram, showing blockages of the background choroidal fluorescence in the placoid lesions (right eye). (B) Right eye, (C) left eye, late phase of the angiogram, showing hyperfluorescence in the placoid lesions and diffuse retinal phlebitis with associated small retinal haemorrhages (arrow).



lesions scattered in the posterior pole and the mid-periphery. The lesions were at the level of the retinal pigment epithelium and choriocapillaris. There was no serous detachment of the sensory retina or pigment clumping. The optic disc, retina, and choroid between these lesions were normal except for widespread abnormalities of the retinal veins, showing extensive distortion, tortuosity, and sheathing. In contrast the retinal arteries appeared virtually normal. Ophthalmoscopic examination of the left fundus showed similar placoid lesions and inflammatory changes of retinal veins associated with small retinal haemorrhages.

Fluorescein angiography in the arterial and arterio-venous phases revealed discrete blockage of the background fluorescence by the whitish-yellow lesions. Later the lesions became gradually fluorescent and progressively hyperfluorescent, so that the periphery of the lesions was stained more prominently, but there was no leakage of dye into the subretinal space. The retinal veins behaved normally in the early phases of the angiography, followed by marked leakages of dye into the surrounding retina

and staining of the large and medium sized vessels in the posterior pole and midperiphery. The retinal phlebitic changes appeared to be independent of the whitish-yellow placoid lesions. Meanwhile the retinal arteries appeared normal on fluorescein angiography (Figs. 1A, B, C).

Systemic corticosteroids with a total dosage of 400 mg prednisolone were given for two weeks. The whitish-yellow lesions gradually resolved over three weeks and were followed by greyish discolouration and pigment clumping in this central area. The widespread retinal phlebitis subsided in a few weeks together with the resolution of the placoid lesions. The macular region of both eyes retained marked pigmentary derangement. Fluorescein angiography performed four weeks after the onset of the disease showed early hyperfluorescence due to window-defect in the periphery of the placoid lesions and hypofluorescence in their centre. The retinal veins were of normal appearance (Fig. 2). Along with the subsidence of the inflammatory changes the visual acuity improved gradually, and three months later it returned to normal in both eyes.

Sixteen months after the onset of the disease the patient returned to us with complaints of paracentral blurred vision in the left eye. On examination there was no substantial change in the right fundus, with sustained normal visual acuity. The left eye still had normal visual acuity, but there was a small paracentral scotoma inferotemporal to the centre. Ophthalmoscopic examination of the left fundus showed subretinal haemorrhages in the pigmentary deranged macular region superonasal to the fovea, followed several weeks later by a haemorrhagic retinal detachment, which eventually extended to the fovea and led to visual acuity loss to 0.2. Fluorescein angiography showed early hyperfluorescence in the macular region, which increased in intensity and area in the course of the angiography, indicating the presence of choroidal neovascularisation, while the choroidal fluorescence was masked in areas of subretinal haemorrhages. Dye leakage from the choroidal neovascular membranes extended into the subretinal spaces in the later stage of the angiography (Figs. 3A, B). In the following months the subretinal haemorrhages were gradually absorbed, leaving proliferated scar tissues with pigment clumpings in the macular region. Six months after the onset of the macular episode the visual acuity remained 0.4.

Physical examination and thorough laboratory survey were repeated several times during the follow-up. The patient kept physically healthy. Haematological tests, urine analysis, and serological tests for various agents including toxoplasmosis and syphilis were negative except for a positive tuberculin skin

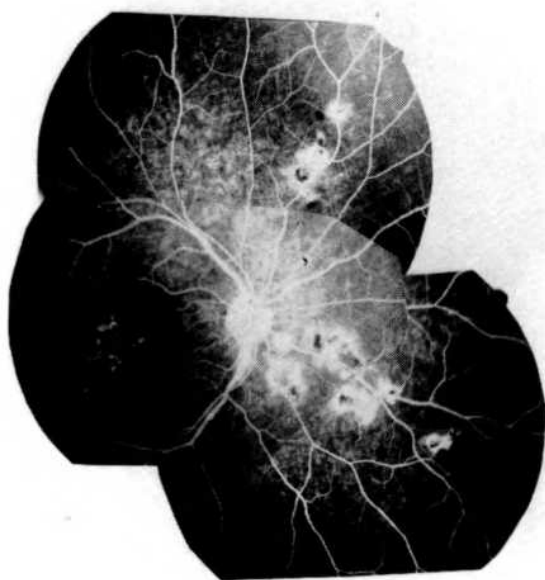


Fig. 2 Fluorescein angiogram recorded four weeks after the onset of disease (right eye), showing window-defect hyperfluorescence in the periphery of the placoid lesions and pigment clumping hypofluorescence in the centre of the lesions. Retinal phlebitis had disappeared.

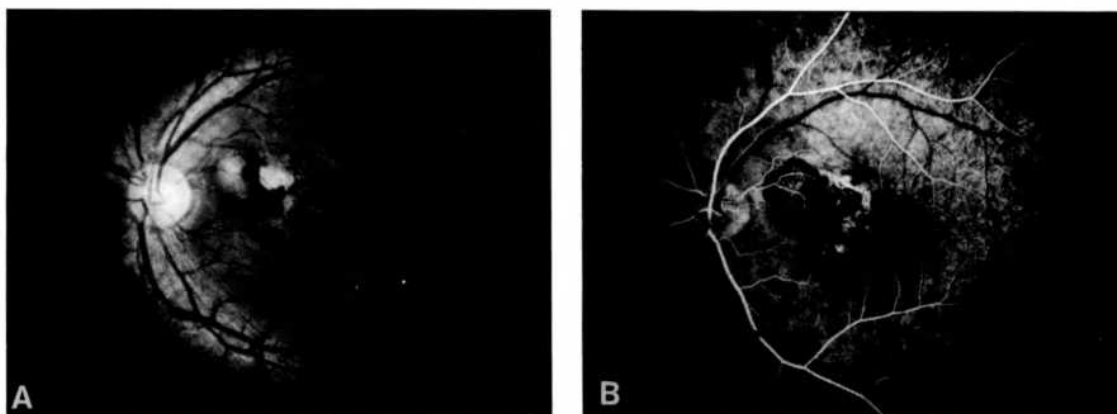


Fig. 3 Fundus photograph (A) and early phase of fluorescein angiogram (B), left eye, recorded 16 months after the onset of disease, showing development of subretinal haemorrhage due to choroidal neovascularisations in the macular region.

test and an increase of cold agglutinin. The cold agglutinin titre was 1024 on the initial examination and 2048 one month later, followed by a return to the normal level (less than 256), and it rose transiently 16 months after the onset of the disease when subretinal macular haemorrhage developed (Table 1).

Discussion

The clinical features, course, and prognosis of this case conform for the most part to acute posterior multiple placoid pigment epitheliopathy, but some findings notable with reference to the pathogenesis of placoid lesions and the late complications of the disease.

The disease has been recognised as an acute inflammatory condition affecting the retinal pigment epithelium and choriocapillaris, though serous detachment of the retina or optic disc swelling are complications in occasional cases. Our case is unusual in that diffuse inflammatory reactions of the retinal vasculature associated with small retinal

haemorrhages occurred in a concurrent but topographically independent manner, with the multifocal placoid lesions at the level of the retinal pigment epithelium and choriocapillaris. It is noticeable that the vasculitis was confined to the retinal veins, and that they subsided dramatically without any residual abnormality. This suggests that any aetiological factor initiating the inflammation may involve both the retinal and choroidal vasculatures. This supports the interpretation that the acute cloudy swelling of the retinal pigment epithelium represents a localised choroidal vasculopathy rather than a primary retinal pigment epitheliopathy.⁷ Retinal vasculitis has been described in occasional cases.^{9,12}

Acute posterior multifocal placoid pigment epitheliopathy is usually benign in nature. The central vision improves rapidly in the first weeks along with resolution of the macular placoid lesions; a more gradual improvement follows even months after cessation of the inflammatory condition, though normal visual acuity may not return when the fovea is damaged severely.¹² A recurrence is rare.^{10,11} Our case showed a typical clinical course, with a rapid inactivation of inflammation and a return to normal visual acuity in both eyes, but it is remarkable that 13 months later the patient again had loss of vision in one eye because of subretinal haemorrhages in the macular region, followed by haemorrhagic macular detachment extending into the fovea. Fluorescein angiography showed choroidal neovascular membranes in the macula.

Gass summarised the results of a long-term follow-up study of 30 cases of the disease and found one case which developed haemorrhagic macular detachment caused by a juxtapapillary choroidal neovascular membrane after recovery of normal visual acuity.⁹ Shatz and associates briefly reported one case which

Table 1 Serum cold agglutinin titre at various times after onset of the disease

Months after onset of disease	Cold agglutinin titre (normal: ≤ 256)
0	1024
1	2048
2	128
3	256
16*	512
17	1024
22	256

*Haemorrhagic macular detachment occurred.

had a focal area of subretinal neovascularisation developed at the margin of a subacute lesion of the disease.¹³

We therefore wish to emphasise that development of a choroidal neovascular membrane is an occasional association of the disease, possibly leading to haemorrhagic retinal detachment. Choroidal neovascular membrane has been shown to form not only in degenerative diseases, including senile macular degeneration, but also in inflammatory diseases.¹⁴ Although the exact mechanism is unknown, it is probable that the subretinal neovascularisation in acute posterior multifocal placoid pigment epitheliopathy represents a late complication rather than a process related to the acute disease. In any event, patients with severe macular pigmentary derangement should be followed up for at least a year after resolution of the inflammatory process. This would provide an early detection of the possible development of choroidal neovascularisation. The present case was not suitable for laser therapy because of the central location of the complication.

The aetiology of acute posterior multifocal placoid pigment epitheliopathy has yet to be defined, but viral infection has been assumed to be responsible in some cases.³⁻⁵ It is noticeable that our case showed raised titres of cold agglutinins in the acute inflammatory stage of the disease. The cold agglutinin titre of the serum is known to rise in acute viral diseases and *Mycoplasma pneumoniae* infection, and the increase may be an isolated laboratory finding or coexist with underlying disease.¹⁵ Our case showed the abnormality as an isolated laboratory finding. The significance of the further rise of the titre long after cessation of the acute disease is not clear, but it occurred coincidentally with the late development of subretinal choroidal neovascularisations.

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Immunological abnormalities in patients with untreated retinal vasculitis

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SUMMARY Peripheral blood immunological features were assessed in 21 patients with clinical and angiographic evidence of retinal vasculitis (RV). Abnormalities of humoral and cellular immunity were frequent in this group of patients. Lymphopenia was the most common immunological abnormality, being present in 76% of patients at presentation ($p < 0.05$). Peripheral blood T and B cells were decreased with a normal helper (OKT4) to suppressor (OKT8) T cell ratio in 11 patients tested (five with Behçet's syndrome and six with idiopathic RV). Significantly increased concentrations of serum immune complexes were present in 55% of patients ($p < 0.05$). Results of the present study indicate the frequent association of peripheral blood immunological abnormalities in patients with active RV and indicate the possible role of immunological mechanisms in its pathogenesis.

The retina is involved in several systemic autoimmune diseases in which the basic pathology is a vasculitis. Retinal vasculitis (RV) is the basic histopathological lesion of Behçet's syndrome¹ and also occurs in polyarteritis nodosa,² giant cell arteritis,^{3,4} and less frequently in SLE.^{5,6} The clinical similarity between RV in this group of diseases and the experimental animal model of RV produced in rabbits^{7,8} suggests that immune complexes may be involved in the pathogenesis.^{11,12}

There has been limited opportunity for the study of immune mechanisms in retinal vasculitis owing to the rarity of the condition and difficulties associated with studying a large group of patients with untreated disease. We present here the results of a study of 21 patients with RV investigated at the onset of their disease before beginning treatment. The results highlight the frequency of immunological abnormalities in untreated patients with RV.

Material and methods

PATIENT SELECTION

Twenty-one patients referred to the Uveitis Research Clinic at Sydney Eye Hospital or the Department of

Immunology, St Vincent's Hospital, were investigated. All patients were seen independently by at least two ophthalmologists and had fluorescein angiograms that were independently reported to be consistent with the diagnosis of RV.

IMMUNOLOGICAL INVESTIGATIONS

Using standard radial immunodiffusion techniques we determined levels of the following serum proteins: IgG, IgM, IgA, C3, and C4. IgE levels were measured by radioimmunoassay (Pharmacia). Functional assessment of the classical and alternative pathways of complement were done by measuring the reciprocal of the titre of serum lysing 50% of sensitised sheep red blood cells (CH50)¹³ and sensitised rabbit erythrocytes (PH50)¹⁴ respectively. Complement assays were performed by the laboratories of Dr J Zeigler and Dr J Charlesworth at Prince of Wales and Prince Henry Hospitals, Sydney.

Serum autoantibodies (antinuclear (ANA), gastric parietal cell (GPC), smooth muscle (SM), and reticulins) were determined by an indirect immunofluorescence technique with a composite block of rat liver and stomach and mouse kidney and stomach as the substrate. DNA binding was determined by the anti-DNA assay kit (Amersham). Serum immune complexes (C1q binding assay and quantitative

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cryoglobulin) were determined by the methods of Andrews *et al.*¹¹ All patients were examined for the presence of serum cryoglobulinaemia, while 11 patients were tested in the C1q binding assay.

Peripheral blood T cell numbers and the percentage of T cells in the two major subsets were analysed by indirect immunofluorescence using monoclonal antibodies (OKT3, 4, and 8; Ortho Diagnostics Systems).¹²

Retinal autoantibodies were detected by indirect immunofluorescence on fresh human retina, removed from previously normal eyes within 12 hours of death. The retina was carefully dissected free from the choroid, folded on itself several times, placed in OCT (Ames Co.), snap frozen in isopentane and solid CO₂, and processed as previously described.¹³

AETIOLOGICAL INVESTIGATIONS

All patients had the following examinations: a full blood count, erythrocyte sedimentation rate, serum and urine biochemical screen, liver function tests, calcium and angiotensin converting enzyme estimations, serological tests for syphilis, toxoplasma, toxocara, cytomegalovirus, herpes simplex, influenza A and B, and adenovirus. Routine chest radiology was performed.

Results

The clinical features of patients with untreated RV are summarised in Table 1. The mean age of onset was 35.0±11.3 years, range 17–54 years. There were

12 females in the study population with a mean age of 38.1 (SD 11.5) years (range 20–54 years) and nine males with a mean age of onset of 31.0 (SD 10.3) years (range 17–44 years). The control population consisted of 161 healthy subjects.

CLINICAL FEATURES

Diagnosis was based on the clinical features with supporting angiographic findings. The clinical features used to diagnose RV were based on those described by ffytche.¹⁷ Patients were considered to have central RV if they had evidence of oedema of the optic nerve head and adjacent retina with or without macular oedema and decreased visual acuity.¹⁴ Patients with peripheral RV had evidence of vascular inflammation without optic nerve head involvement and usually confined to veins more than two disc diameters away from the optic nerve. Fourteen patients (eight males and six females) had peripheral RV with a mean age of onset of 32.9 (SD 11.0) years (range 17–47 years). In two cases there was combined central and peripheral RV (one male and one female). Five patients (all of whom were female) had central RV with a mean age of 39.0 (SD 11.5) years (range 21–54). The fundal appearance in central RV was characterised by disc oedema with venous dilatation, perivenular haemorrhages, and vascular sheathing confined to the region of the optic disc. Macular oedema with decreased visual acuity was present in all five patients. Hypertension and raised intracranial pressure were excluded. All cases of central RV cases (9 and 18) had associated uveitis

Table 1 Clinical features in 21 patients with retinal vasculitis

Patient	Sex	Age	Duration (months)	Bilateral	Peripheral or central	VA <6/12	Associated uveitis	Associated systemic disease
1	M	37	18	+	P	+	PU	Sarcoidosis
2	M	40	6	—	P	—	PU	Idiopathic
3	M	26	13	—	P	—	*PU	Idiopathic
4	M	17	24	+	P	+	*PU	Idiopathic
5	F	32	27	—	C	+	*PU	Idiopathic
6	F	36	49	+	C+P	+	*PU	Behçet's
7	F	52	22	+	P	+	AU+PU	Idiopathic
8	F	30	15	—	P	+	*PU	Idiopathic
9	F	54	53	—	C	+	AU+PU	Behçet's
10	M	28	16	+	P	+	AU+PU	Behçet's
11	F	20	7	—	P	+	PU	Behçet's
12	M	43	24	—	P	—	AU+PU	Behçet's
13	M	44	3	+	C+P	+	*PU	Idiopathic
14	M	18	3	—	P	—	*PU	Idiopathic
15	F	41	21	—	C	+	*PU	SLE
16	F	45	11	—	P	+	*PU	SLE
17	F	48	8	+	P	+	PU	Idiopathic
18	F	47	25	—	C	+	AU+PU	Behçet's
19	M	26	2	—	P	—	*PU	Idiopathic
20	F	31	36	+	P	+	AU+PU	Behçet's
21	F	21	15	—	C	+	*PU	Idiopathic

AU=anterior uveitis PU=posterior uveitis SLE=systemic lupus erythematosus *PU=chororetinal lesions

with vitreous inflammatory cells. One patient with Behçet's syndrome (case 18) developed severe thrombotic glaucoma requiring enucleation. All patients with central and central combined with peripheral RV had decreased visual acuity at presentation (Table 1).

DISEASE ASSOCIATIONS

Relevant associated diseases were present in 10 of 21 patients with RV (Table 1). Behçet's syndrome was the most common disease association, being present in seven patients (five females). It was diagnosed by the presence of oral and genital ulcers and the absence of any other cause.¹⁹ RV was confined to the peripheral veins in four patients with Behçet's syndrome (Fig. 1), with two patients having central RV and one patient having panretinal involvement (Fig. 2).

Two patients had SLE diagnosed on the basis of American Rheumatism Association criteria²⁰ and the presence of significantly raised titres of DNA antibodies. Both patients were females and had symptoms suggestive of SLE for the previous five years. In each case RV was severe, with decreased visual acuity.

IMMUNOLOGICAL INVESTIGATIONS

Serum IgG levels were significantly reduced in five patients (range 6.1–6.8 g/l ($p < 0.05$)). One patient had an increased serum IgA, while four had significantly raised serum IgM levels ($p < 0.05$), and six patients had raised serum IgE levels compared with the control population ($p < 0.05$).

Serum complement levels (C3 and C4) were

normal or slightly increased in all patients with RV (Table 2). Increased C4 levels were detected in the serum of eight patients tested, while C3 levels were raised in only one patient, who also had an increased C4 level. The mean C3 level was 1.3 (SD 0.3) g/l (range 0.9–2.0) and for C4 the mean was 0.3 (SD 0.1) g/l (range 0.1–0.6). Primary complement deficiency was excluded, as all patients had a normal or raised CH50 (mean 286 (SD 64) units, range 200–400).

Autoantibodies were present in the serum of nine patients (Table 2). Three patients (Nos. 1, 7, and 13) had low titre reticulin antibodies (1/10), while an additional three patients (Nos. 3, 4, and 17) had low titre smooth muscle antibodies ($\leq 1/40$). Significantly raised serum autoantibody titres were present in three patients, two with SLE (cases 15 and 16) who had raised antinuclear antibodies and increased DNA binding before treatment, one of whom also had a high titre of gastric parietal cell antibodies and a third patient (case 8) with idiopathic RV had a rheumatoid factor titre of 1/80. None of the five patients or nine controls tested had autoantibodies to human retina by indirect immunofluorescence.

A comparison of the immunoglobulin abnormalities in different aetiological groups of patients with RV is summarised in Table 3, which demonstrates the increased frequency of peripheral blood immunological abnormalities in patients with idiopathic RV and Behçet's syndrome. Seven patients had significantly raised cryoglobulin levels when compared with controls ($p < 0.005$). Of these, three had Behçet's syndrome, three had idiopathic RV, and one SLE (Table 3). The mean C1q binding level was 12.4 (SD 7.3)% (range 5–40%) and this was significantly increased in comparison with the control group (mean 6.5 (SD 5.6)%, range 1–18%). Six patients had raised C1q binding levels, three with Behçet's



Fig. 1 Patient 11. A 20-year-old female with recurrent mouth and genital ulcers. Fundus photograph of peripheral retinal vasculitis involving the superior temporal veins.

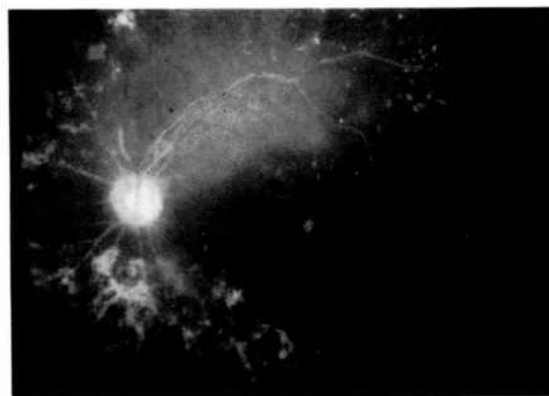


Fig. 2 Patient 6. A 36-year-old female with Behçet's syndrome. The patient has panuveitis with central and peripheral retinal vasculitis.

Table 2 Immunological findings in 21 patients with retinal vasculitis

Patient	ESR (mm/h)	Lymphocytes absolute no. (cells/mm ³)	Immunoglobulin level				Complement			Autoantibodies
			IgG (g/l)	IgA (g/l)	IgM (g/l)	IgE (U/ml)	C3 (g/l)	C4 (g/l)	CH50 (units)	
1	5	1742	15.0	1.1	1.5	120	0.9	0.4	260	Retic 1/10
2	12	1300	8.7	2.7	0.9	60	1.5	0.3	240	—
3	1	1420	6.6	0.9	3.0	30	1.1	0.2	200	SM 1/10
4	13	1346	12.0	1.6	0.9	317	1.4	0.3	243	SM 1/10
5	6	1506	7.3	1.1	0.8	6	1.2	0.3	375	—
6	21	960	10.0	2.1	3.5	80	1.1	0.4	NT	—
7	12	890	6.1	1.6	1.1	70	2.0	0.6	400	Retic 1/10
8	3	840	10.0	1.2	1.3	68	1.2	0.4	234	RF 1/80
9	12	1125	6.8	1.2	1.1	220	1.0	0.3	NT	—
10	4	670	16.0	4.0	2.0	218	0.9	0.2	367	—
11	1	1820	8.5	1.5	2.7	18	1.2	0.3	246	—
12	7	1230	12.5	1.5	1.7	108	1.3	0.2	>400	—
13	5	1170	7.6	2.4	0.8	730	1.2	0.4	225	Retic 1/10
14	1	1112	11.2	1.6	1.3	240	1.4	0.2	280	—
15	4	1300	8.3	2.4	1.4	140	1.0	0.1	200	ANA 1/640, DNA 30, GPC 1/640
16	14	2240	9.3	1.4	1.0	146	1.5	0.4	340	ANA 1/160, DNA 24
17	21	1600	13.0	3.1	0.9	35	1.3	0.2	294	ANA 1/40, SM 1/10
18	12	260	6.7	2.0	0.9	120	1.4	0.2	340	—
19	2	860	12.0	1.3	1.2	80	1.6	0.3	NT	—
20	6	1260	6.7	1.1	0.8	334	1.5	0.4	280	—
21	18	840	11.0	1.2	2.3	125	1.5	0.4	320	—
mean±2SD	9 ±6	1217* ±438	9.8 ±2.8	1.8 ±0.8	1.5 ±0.8	174* ±175	1.3 ±0.3	0.3 ±0.1	286 ±64	
Controls (n=161)	11 ±9	2920 ±765	10.9 ±3.6	2.0 ±1.8	1.3 ±0.8	45 ±103	1.1 ±0.6	0.2 ±0.1	300 ±100	
mean±2SD										

Abnormal results are printed in bold face.

* $p < 0.05$ (patients with RV compared with controls, Student's *t* test)

NT=not tested RF=rheumatoid factor. GPC=gastrointestinal cell. Retic=reticulin antibody ANA=antinuclear antibody. SM=smooth muscle antibody DNA=DNA binding.

SI conversion lymphocytes/mm³ × 10⁶=lymphocytes/μl U/ml × 1000=U/l

syndrome (cases 11, 12, and 18), two with idiopathic RV (cases 3 and 13), and one SLE (case 16). Five patients had both increased cryoglobulins and C1q binding. Four of the seven RV patients with Behçet's syndrome had increased circulating immune complexes compared with controls ($p < 0.05$). Serum

immune complex levels paralleled disease activity and fell to normal levels in seven of the RV patients repeatedly tested after the institution of effective treatment.

The mean peripheral blood lymphocyte count was 1.22 (SD 0.44) × 10⁹/l (range 0.26 – 2.24 × 10⁹/l) and

Table 3 Comparison of immunological abnormalities in retinal vasculitis according to disease association

Disease associations	Patient no	Immunoglobulin levels				Immune complexes	Lymphopenia (<1500 cells/mm ³)
		↓ IgG	↑ IgA	↑ IgM	↑ IgE		
Idiopathic	2,3,4,5,7,8 13,14,17,19,21	*2	0	2	3	5	9
Behçet's syndrome	6,9,10,11,12 18,20	3	1	2	3	6	6
SLE	15,16	0	0	0	0	2	1
Sarcoidosis	1	0	0	0	0	0	0

*Figures refer to the number of patients having a particular immunological abnormality in each group SI conversion. cells/mm³ × 10⁶=cells/μl

this was significantly lower than the value for controls ($p < 0.005$), with 16 patients having lymphopenia (< 1500 cells/mm³) at presentation ($p < 0.005$). T cell subset numbers were measured in six patients with idiopathic RV and five with Behçet's syndrome by means of monoclonal antibodies. The percentage of T cells (OKT3) was 72% (SD 10%) for patients with idiopathic RV, 78% (SD 15%) for patients with Behçet's syndrome, and 77% (SD 12%) for controls. The T cell ratios of OKT4 to OKT8 cells were 2.0 and 1.8 respectively, which were similar to the value for the control group (1.9).

Discussion

Although a large variety of systemic diseases have been described in patients with retinal vasculitis, recent information suggests that only a small proportion of these diseases occur with a significant frequency in association with RV. In agreement with the findings of Dumonde *et al.*¹² and Andrews *et al.*¹¹ Behçet's syndrome was the most frequent disease seen in patients with RV, together with SLE and sarcoidosis. These diseases are idiopathic, with prominent immune abnormalities and a presumed immunological basis. The results of the present study support the concept that RV is an immunologically mediated disease.

Immunoglobulin abnormalities in RV were first reported by Koliopoulos *et al.*²¹ and their observation of a raised serum IgM level in this disease was subsequently confirmed by Chilman²² and is similar to the findings of the present study. In contrast to previous studies, this study showed a significantly increased frequency of raised serum IgE levels and decreased IgG levels in patients with RV. These changes have not previously been reported in patients with RV. Raised IgE levels could be attributed to associated allergic diseases in two patients; the remaining four patients had no obvious cause for a raised IgE level and it was not associated with a peripheral blood eosinophilia.

The presence of circulating immune complexes (CIC) in a high proportion of patients with RV was first reported by Andrews *et al.*¹¹ and subsequently by Dumonde *et al.*¹² The results of the present study confirm these earlier studies with 55% of patients tested having significantly increased serum immune complexes as detected by the C1q binding assay and 33% having cryoglobulinaemia. Immune complexes were more frequently detected in the sera of patients with associated diseases, particularly Behçet's syndrome, and were more often present in the sera of patients with associated uveitis and peripheral RV. No definite aetiological agent was identified in patients with RV, and there were no antigens which

could be incriminated in immune complex formation, with the possible exception of DNA antibodies in patients with SLE.

Serum complement levels (C3 and C4) and total haemolytic complement were either normal or increased in all patients with RV. The raised levels may reflect the role of these proteins as acute phase reactants, similar to the observed increased α -1 antitrypsin levels recently reported by us in patients with active RV.²³ Primary complement deficiency has been reported in several forms of vasculitis, including SLE.²⁴ Andrews *et al.*¹¹ reported decreased C3 levels in 24% of 17 patients with RV, and Dumonde *et al.*¹² reported complement abnormalities of 'non-specific type' in the majority of their patients. These discrepant results may be due to several factors, including the timing of serum sampling, treatment regimen and the presence of an associated systemic vasculitis.

Other retinal autoantibodies have recently been reported in patients with RV.²⁵ This is of considerable interest in view of the fact that experimental RV may be induced in certain primates following immunisation with retinal S antigen and the demonstration of subsequent development of serum retinal antibodies in these animals.²⁶ Five patients with untreated RV were tested at presentation for the presence of retinal antibodies by an indirect immunofluorescent technique with human retina as the substrate. Retinal antibodies were not detected in this assay. The difference between these results and those of Dumonde *et al.*¹² may be due to differences in methodology or may reflect the fact that such antibodies develop only after prolonged or severe ocular inflammation. Autoantibodies, including smooth muscle (SM), antinuclear (ANA), and gastric parietal cell (GPC) antibodies, have been reported previously in patients with RV.^{11,12} With the exception of the presence of antinuclear antibodies, which suggest an underlying connective tissue disease such as SLE, the significance of other autoantibodies in RV is obscure. They may be an epiphenomenon or reflect ocular tissue damage, for example to vascular smooth muscle. Alternatively these immunological findings may reflect an immunoregulatory abnormality with increased B cell activity secondary to change in regulatory T cell subsets (T_H and T₃), as has been proposed in other vasculitides such as SLE.^{24,28}

This concept is supported by the observation that lymphopenia was the most common immunological abnormality at presentation, being detected in 16 patients. In the subsets of patients tested both T and B lymphocytes were decreased, and there was no change in the ratio of helper to suppressor T cells. Although lymphopenia is a common manifestation of certain other vasculitic syndromes, such as SLE,²⁴ it has not previously been reported in patients with RV.

Lymphopenia was observed in 55% (6/11) of patients with circulating immune complexes and the same proportion of patients with autoantibodies, while all patients with raised serum IgE levels were lymphopenic. Changes in T cell subsets may help to explain these observations, which may be secondary to a decrease in specific immunoregulatory T cells. Several mechanisms may be envisaged to explain this observation, including the presence of lymphocytotoxic antibodies, and this possibility is being examined.

The recent realisation of the association of RV with the HLA DR4 antigen²⁷ indicates an immunogenetic predisposition to this disease, while the results of the present study in a small group of untreated patients with RV confirm the frequency of peripheral blood immunological abnormalities, especially immune complexes and lymphopenia, in this previously enigmatic disease and indicate the possible role of autoimmune mechanisms in the pathogenesis of retinal vasculitis.

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Serum autoantibodies and uveitis

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SUMMARY The serum of 893 uveitis patients was examined for various non-ocular specific autoantibodies. Overall 40.8% of patients had detectable levels of autoantibodies in their sera. These comprised antibodies to smooth muscle (23.1%), nuclear material (12.7%), gastric parietal cell (3.0%), reticulin (1.8%), and mitochondria (0.2%). When the patients were distributed into nine selected categories of uveitis, only patients with one distinct clinical entity showed a statistically significant difference in the presence of the above serum autoantibodies as compared with healthy individuals. They were patients with uveitis associated with juvenile chronic arthritis, among whom antinuclear antibody was detected in 77% ($p < 0.001$). Testing for the presence of circulating non-ocular specific autoantibodies appears to be of little or no value in the routine screening of uveitis patients, but it may be helpful in the diagnosis and management of certain individual cases, such as juvenile chronic arthritis, or as a research tool to advance understanding of pathogenetic mechanisms.

Uveitis comprises a complex group of diseases, of which the aetiopathogenesis is often unknown. Although recent evidence reveals underlying immunological aberrations in a large number of patients,^{1,2} the exact relationship between non-ocular specific serum autoantibodies and uveitis is not clear, the literature^{3,4} being limited and contradictory.

In view of the puzzling nature of uveitis and that it may form part of a systemic disease process, many patients are frequently overinvestigated by being subjected to a vast battery of unnecessary tests.

A large patient population was examined, therefore, to determine whether circulating non-ocular specific autoantibodies have a significant role to play in the aetiopathogenesis of uveitis.

Materials and methods

This study involved 893 patients with uveitis seen at Moorfields Eye Hospital between July 1977 and December 1982. The patients were distributed into nine selected categories of uveitis: acute anterior, chronic anterior, pan, posterior, intermediate, heterochronic cyclitis, juvenile chronic arthritis, Behçet's disease and Vogt-Koyanagi-Harada syndrome. Criteria laid down by the International Uveitis Study Group⁷ were used for the classification.

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Circulation antibodies to nuclear material, smooth muscle, gastric parietal cells, reticulin, and mitochondria were detected by a standard indirect immunofluorescence technique using a Zeiss epifluorescence microscope equipped with the appropriate interference filters. Normal values were determined from 100 healthy individuals.

Statistical analysis was by the χ^2 method on 2×2 frequency tables with Yates's correction.

Results

Of the 893 patients studied the majority (53%) belonged to the acute anterior uveitis category (Table 1.)

Overall 40.8% of the patients had detectable levels of non-ocular specific autoantibodies (titre < 1.50) in

Table 1 Selected categories of uveitis in 893 patients

Classification	Number	Percentage
Acute anterior	469	53
Posterior	129	14
Pan	115	13
Chronic anterior	72	8
Intermediate	47	5
Heterochronic cyclitis	23	3
Behçet's disease	20	2
Juvenile chronic arthritis	13	1.5
Vogt-Koyanagi-Harada syndrome	5	0.5

Table 2 Serum autoantibodies in selected categories of uveitis

Classification	Autoantibody (titre <1:50)									
	ANA		ASMA		AGPCA		ARA		AMA	
	No.	%	No.	%	No.	%	No.	%	No.	%
Healthy individuals	15	15	16	16	3	3	2	2	0	0
Acute anterior	47	10	116	25†	19	4	7	1.5	1	0.2
Posterior	13	10	35	27‡	2	1.5	3	2	0	0
Pan	24	21	25	22§	3	2.6	3	2.6	1	0.9
Chronic anterior	7	10	12	17	2	3	1	1	0	0
Intermediate	4	8.5	8	17	0	0	2	4	0	0
Heterochromic cyclitis	5	22	4	17	1	4	0	0	0	0
Behçet's disease	3	15	4	20	0	0	0	0	0	0
Juvenile chronic arthritis	10	77*	1	8	0	0	0	0	0	0
Vogt-Koyanagi-Harada syndrome	0	0	1	20	0	0	0	0	0	0
Overall	113	12.7	206	23.1	27	3	16	1.8	2	0.2

ANA: antinuclear antibody. ASMA: antismooth muscle antibody. AGPCA: antigastriac parietal cell antibody. ARA: antireticulin antibody. AMA: antimitochondrial antibody.

* $p < 0.001$.

† $p > 0.1$ (NS).

‡ $p > 0.05$ (NS).

§ $p > 0.1$ (NS).

their serum. Although antismooth muscle antibody (ASMA) and antinuclear antibody (ANA) were the most frequently detected, 23.1% and 12.7% respectively, patients in only one of the uveitis categories showed a statistically significant difference in the incidence of autoantibodies as compared with healthy persons. These were patients with uveitis associated with juvenile chronic arthritis; 77% had ANA in their serum ($p < 0.001$) (Table 2).

Discussion

Uveitis may occur as an isolated event or as a manifestation of a systemic immuno-inflammatory disease process, for example, sarcoidosis and Behçet's disease. Intraocular inflammation can develop as a result of the breakdown of regulatory immune mechanisms, which may in some cases lead to autoimmune disease involving the production of circulating autoantibodies to ocular and non-ocular structures.

The results of this study are mostly in agreement with the findings of Kijlstra *et al.*,⁶ who were unable to show any association between non-ocular specific autoantibodies and various types of uveitis. Significant associations were reported, however, by Rahi *et al.*,⁵ but the numbers of their patients were so small they were unable to draw any firm conclusions from their study. The finding of ANA in the serum of 77% of patients with juvenile chronic arthritis ($p < 0.001$) is in agreement with that of previous studies.^{8,9}

Recent work postulates that autoimmunity may be the result of anti-idiotypic antibodies (that is, to the

shape of the antigen binding regions) of viral antibodies,¹⁰ or occurring via mechanisms involving cross-reactive idiotypes¹¹—for example, microorganisms or structures of a microbial agent. This may be relevant, as many infective agents have been implicated in the pathogenesis of uveitis; they include viruses,¹² chlamydia,¹³ and klebsiella.¹⁴

The two stages in the generation of autoimmune disease are, first, the initiation state (that is, the development of autoantibodies or autoreactive lymphocytes), then the development of tissue damage due to immune responses. Whether the initial induction of autoreactive B and T cells leads to autoimmune disease would depend on factors such as abnormalities of the suppressor T cell pathway reported to coexist with autoimmunity and necessary to induce autoimmune disease in mice.¹⁵ Defective suppressor T cells have been reported in acute anterior uveitis^{1,16,17} and heterochromic cyclitis,¹ and this defect may lead, via B cell overstimulation, not only to the production of autoreactive B and T cells but also to high levels of serum immunoglobulins and low affinity antibodies, which may be involved in immune-complex mediated inflammation. Raised levels of serum IgA¹⁸ and circulating immune complexes^{2,4} have been found in various types of uveitis. Autoantibodies to ocular structures have also been found in uveitis. These include antibodies to retinal 'S' photoreceptor antigen,² corneal epithelium,³ and lens crystallins (unpublished observation).

In conclusion, there seems little benefit in the routine screening of patients with uveitis for the presence of circulating non-ocular specific autoanti-

bodies. It may be of value in individual cases, as in the diagnosis and management of uveitis associated with juvenile chronic arthritis or for research purposes to advance understanding of immuno-pathogenetic mechanisms.

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Cryotherapy for retinopathy of prematurity: timing of intervention*

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SUMMARY This is a retrospective study of the results of cryotherapy for retinopathy of prematurity in 30 eyes of 17 patients from November 1976 to March 1983. The report is in the language of the international classification of retinopathy of prematurity. Ten eyes were treated at stage 4 disease, seven eyes at severe or late stage 3 'plus' disease, and 13 eyes at moderate or mid-stage 3 'plus' disease. All eyes had the cryotherapy applied to the ridge and the extraretinal fibrovascular proliferation contiguous with the ridge, some with additional treatment of the avascular retina. The results show that this method of treatment must be applied before severe stage 3 'plus' disease is established in order to prevent visual disability and minimise retrolental fibroplasia. The treatment of the selected cases of progressive moderate stage 3 'plus' disease accomplished those objectives.

Severe retinopathy of prematurity (ROP) resulting in cicatricial disease or retrolental fibroplasia (RLF) is still a major cause of blindness and visual disability in infancy.¹ All attempts at its complete medical prevention have failed. The efficacy of vitamin E has been under extensive investigation, with varied reports of its effect on the incidence and severity of retinopathy of prematurity.^{2,3} Total elimination of visual disability and blindness following retinopathy of prematurity is still an elusive goal.

Surgical intervention in selected severe progressive cases of retinopathy of prematurity has been recommended in the report of the Joint Committee for the Study of Retrolental Fibroplasia in Japan.⁴ Support for surgical intervention has been presented outside Japan.⁵⁻¹⁴ Others have concluded that treatment was of no apparent benefit¹⁵⁻¹⁸ or possibly effective in a few cases but generally not effective or perhaps deleterious.¹⁹ Although some have attempted to control their studies by treating one eye,²⁰⁻²² significant evidence has not been produced to resolve the controversy.

Resolution of this dichotomy of opinion has been impaired by the inability accurately to identify those

severe cases of retinopathy that will predictably result in visual disabling retrolental fibroplasia. In addition, the profusion of terminology and different classifications has made the comparison of results virtually impossible.

This retrospective study attempts to provide additional support for surgical intervention, with particular reference to the timing of intervention based on the appearance and progression of the acute disease.

The terminology used here is that of the international classification.²³ However, during the period of this study no distinction was made between a demarcation line (stage 1) and a ridge (stage 2). Stage 3, extraretinal fibrovascular proliferation, is subdivided as follows. Stage 3a has small aggregates of extraretinal fibrovascular proliferation appearing on the posterior aspect of the ridge and giving a ragged appearance to it. Stage 3b has an arc of confluent extraretinal fibrovascular proliferation on the posterior aspect of the ridge, even obscuring it with extensive proliferation; stage 3b may have riders or extensions posteriorly; it is pink in its progressive phase, losing its colour as involution or fibrosis occurs. Stage 3c is the latest and most severe manifestation and is heralded by the appearance of a sheet or membrane of small vessels extending from the internal surface of the confluent extraretinal fibrovascular proliferation, into the vitreous, perpendicular to the retina, and/or posteriorly along the retina.

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Table 1 Characteristics of 17 patients and timing of progression and treatment of retinopathy

Patient	Year of birth	Gestational age (weeks)	Birth weight (g)	Chronological (adjusted*) age in days at first observation of stage				
				Eye 1 & 2	3	3+	4-4+	At cryotherapy
1	76	30	1165	R		68 (-2)		72 (2)
				L		68 (-2)		72 (2)
2	77	26	825	R 58 (-40)	74 (-24)		102 (4)	103 (5)
				L 58 (-40)		74 (-24)	102 (4)	103 (5)
3	77	26	880	R	70 (-28)	112 (14)		114 (16)
				L	70 (-28)			None
4	79	27	925	R	66 (-25)	73 (-18)		91 (0)
				L	66 (-25)	73 (-18)		85 (-6)
5	79	30	960	R		63 (-7)	71 (1)	66 (-4)
				L		63 (-7)		66 (-4)
6	79	28	1140	R		48 (-36)	73 (-11)	73 (-11)
				L		48 (-36)		68 (-16)
7	79	27	755	R 54 (-37)		80 (-11)		80 (-11)
				L 70 (-21)		80 (-11)		80 (-11)
8	80	29	1460	R 40 (-37)	60 (-17)	71 (-6)		71 (-6)
				L 40 (-37)	60 (-17)	71 (-6)		71 (-6)
9	81	30	1600	R 32 (-38)	45 (-25)	52 (-18)	59 (-11)	59 (-11)
				L 32 (-38)	45 (-25)	59 (-11)		59 (-11)
10	81	26	780	R		60 (-38)	99 (1)	101 (3)
				L 46 (-52)		60 (-38)	95 (-3)	101 (3)
11	81	26	760	R 69 (-29)		76 (-22)	99 (1)	101 (3)
				L 69 (-29)		76 (-22)	101 (3)	101 (3)
12	81	25	620	R 66 (-39)		80 (-25)	86 (-19)	86 (-19)
				L 52 (-53)		82 (-23)		None
13	82	25	630	R		65 (-40)		81 (-24)
				L	65 (-40)	72 (-33)		96 (-9)
14	82	26	900	R 33 (-65)	47 (-51)	67 (-31)		69 (-29)
				L 40 (-58)	47 (-51)	57 (-41)		69 (-29)
15	82	26	660	R 60 (-38)	83 (-15)			None
				L 53 (-45)		83 (-15)		88 (-10)
16	82	25	810	R 44 (-61)		83 (-22)		84 (-21)
				L 44 (-61)		83 (-22)		84 (-21)
17	82	25	660	R 45 (-60)	66 (-39)			None
				L 45 (-60)	66 (-39)	78 (-27)		82 (-23)
Average		27	914		50 (-45)	62 (-30)	71 (-19)	89 (-3)
								83 (-8)

* Adjusted age = [(days since birth) - (days premature at birth)]

In the international classification 'plus' disease means dilatation of the veins and tortuosity of the arteries in zone I. Plus disease may occur in one or more quadrants of zone I and may not be observed in the posterior pole vessels supplying sectors without serious retinopathy in zones II or III.

Cicatrical disease or retrolental fibroplasia is graded as described by Owens.²¹

Patients and methods

From November 1976 to March 1983, 30 eyes in 17 patients had cryotherapy for stage 3+b to 4+ retinopathy of prematurity. In five years of this period 328 eyes with stage 1 to 4+ retinopathy were identified in infants under 1500 g birth weight. Twenty-five eyes, or 7.5%, were treated. 34% of the eyes reaching stage 3+ and 100% of the eyes reaching 4-4+ were treated. By birth weight group 12% of all

eyes with any ROP were treated in infants under 1000 g at birth and 3.5% in infants 1000 to 1499 g.

Characteristics of the 17 patients and the timing of progression of disease are shown in Table 1. Patients 1 to 8 have been included in a previous report.¹⁴

Contrary to common practice, infants at risk are currently screened and followed up by direct ophthalmoscopy through the infant gonioscopy lens (Layden infant gonioscopy lens: Ocular Instruments Inc., 12100 Northrup Way, Bellevue, Washington, 98005). The examination can be conducted at any time with minimal inconvenience to the infant and the nursery staff and with atraumatic control of the ocular position. Examination of the retina to the ora serrata throughout 360° is usually possible. Photographic representation of the disease can be achieved with a hand-held fundus camera through the same gonioscopy lens. Indirect ophthalmoscopy is also employed through the gonioscopy lens, and by the

Table 2 Preoperative and early postoperative observations at 1st (second) treatment

Patient	Eye	Adjusted age (days)	Stage of retinopathy	Location* of cryotherapy	Postop comments†
1	R	2	3+?	1212, AR	
	L	2	3+?	1212, AR	RD 0801
2	R	5	4+	1212, AR	RD 0711
	L	5	4+	1212, AR	RD 0105
3	R	16	3+b	0712, AR	
	L		3?	none	
4	R	0	3+b	1212	
	L	-6 (1)	3+b	1212 (10)	
5	R	-4 (1)	3+c (4+)	0708 (1212)	(EFP periauric)
	L	-4 (1)	3+c	1212 (?)	
6	R	-11	4+	1212	h
	L	-16 (11)	3+c	1212 (03, 08)	RD 0105, h
7	R	-11 (-6)	3+c	1212 (09)	h
	L	-11 (-6)	3+c	1212	h
8	R	-6	3+b	0204, 0711	h
	L	-6	3+b	0711	
9	R	-11	4	0711	
	L	-11	3+b	0103, 0405	RD 0305
10	R	3	4+	1212	Hyphaema
	L	3	4+	1212	Hyphaema
11	R	3	4+	0711	RD 0710, h
	L	3	4+	0205	RD 0204, h
12	R	-19	4+	0806, AR	RD 0912, h
	L		3+?	none	
13	R	-24 (-9)	3+c	1212, AR	h, Cryotherapy Posterior to ridge
	L	-9	3+c	0205, 0711	
14	R	-29	3+b	0806	h
	L	-29	3+b	1212	h
15	R		3b	none	
	L	-10	3+b	0206, 0709	h 0810
16	R	-21	3+b	0612, 0304	h
	L	-21	3+b	0103, 0406	h
17	R		3b	none	
	L	-23	3+c	0711	h 0711

* Radial distribution in clock hours, clockwise in each eye. E.g., 0712 = from 7 o'clock to 12 o'clock; AR = avascular retina treated.

† EFP = extraretinal fibrovascular proliferation; h = haemorrhage, RD = retinal detachment.

? = Could not be determined from records

usual technique, but scleral indentation is not used in the nursery. Scleral indentation is difficult for sustained viewing, distorts the disease by vascular compression, and can cause haemorrhages from the fragile extraretinal fibrovascular proliferation.

Mydriasis in patients up to six months of adjusted age is accomplished with a combination of cyclopentolate (0.2%) and phenylephrine (1.0%) instilled 45 minutes and 30 minutes prior to the examination. Topical proparacaine hydrochloride (0.5%) is instilled prior to lens placement.

All at-risk infants are first examined at 4 to 5 weeks of age. The examination is repeated every two weeks until retinopathy is not anticipated or the retina is fully vascularised. If retinopathy is observed, the eyes are examined weekly. When stage 3 retinopathy appears they are examined more frequently as dictated by the severity. When regression of disease is clearly evident, the eyes are examined at dis-

cretionary intervals of two weeks or more until the retinopathy is completely resolved and retinal vascularisation is complete.

The eyes were not selected for treatment on the basis of stage of disease prospectively. My attempts to determine signs of resolution, along with errors in timing of examination or treatment, resulted in the eyes being treated having reached three distinctly different stages or substages of disease.

Table 2 shows the most advanced stage of disease reached and the location of therapy. Table 3 shows a more detailed breakdown of the circumferential extent of disease, with subgradation of stage 3 disease at the time of treatment in patients 10 to 17. The use of a proposed international classification²² and a documentation system²³ since 1 December, 1981 has enabled more precise determination of qualitative and quantitative progression of disease.

Cryotherapy was applied under general anaes-

Table 3 Location* of retinopathy and treatment at first cryotherapy, patients 10 to 17

Patient	Location		Cryotherapy			
	Eye	Stage of retinopathy				
		3+a	3+b	3+c	4-4+	
10	R		1107		0711	1212
	L			0511	0205	1212
11	R				0711	0711
	L				0205	0205
12	R	0206	0809		0912	0806
	L					None
13	R	1002, 0507	0205	0710		1212
	L			0105, 0711		0205, 0711
14	R	0304, 1102	0203, 0711			0806
	L	1206, 0912	0709			1212
15	R					None
	L		0207			0206, 0709
16	R		0612			0612, 0304
	L		1206			0103, 0406
17	R					None
	L	0205, 0708, 1011	0809	0910		0711

* Radial distribution, clockwise in each eye.

thesia in an operating room. The standard retina probe was found to be too large. A cataract probe was used. Even this has been modified by placing a thinner silicone shield over the slightly curved probe leaving 2 mm of the 1.5 mm diameter tip exposed. Although the disease to be treated was usually located in zone II, we have not had to open the conjunctiva, and a sterile field is not necessary.

A previously reported histopathology clinical correlation on the eyes of patient 1 established the premise that the ridge-extraretinal fibrovascular proliferative complex should be treated.⁷ We have mainly adhered to that principle in patients 4 to 17. The ridge-extraretinal fibrovascular proliferative complex is straddled and the freezing is continued until the ice ball reaches the innermost surface. If there is doubt about effective freezing, a second freeze is applied. Extraretinal fibrovascular proliferations posterior to the ridge, or isolated from it, are not treated. A single continuous row of cryotherapy is applied to the arc of stage 3+b or worse retinopathy in addition to any stage 3 disease in continuity with it.

The treated eyes were put on 1% atropine ointment once daily and chloramphenicol-hydrocortisone ophthalmic ointment twice daily for five to seven days.

Results

Two patients developed significant bradycardia during the procedure. The anaesthetist asked for the procedure to be stopped after the left eye had been

treated in patient 5. Five days later the innermost extension of the extraretinal fibrovascular proliferation could not be frozen in some sectors of the right eye because serous detachment had developed.

During treatment of stage 3+c retinopathy indentation caused the intravitreal vessels to collapse, but they became visible during the freezing. As the ice ball defrosted, a small localised haemorrhage frequently appeared at the internal surface of the extraretinal fibrovascular proliferation.

In the early postoperative period a variable degree of lid oedema prevented examination for up to 48 hours. At the first possible examination 'plus' disease was markedly diminished if the extraretinal fibrovascular proliferation had been effectively treated. Iris hyperaemia disappeared as rapidly. The pupillary vascular membrane, which was frequently present at treatment, disappeared more slowly. The extraretinal fibrovascular proliferation could not usually be recognised, but small haemorrhages could frequently be seen over the cryotherapy spot. A small serous detachment sometimes occurred posterior to the cryotherapy in the most florid 'plus' cases.

In patient 10, the only patient treated with a retina cryoprobe, the disease was entirely peripheral, and bilateral hyphaemas appeared postoperatively. They cleared spontaneously, leaving areas of iris atrophy. The unrecognised extent of the larger ice ball was probably directly responsible for this complication.

The peripheral haemorrhages, originally of some concern, resolved over a period of one to five weeks. All the detachments left a posterior pigment line, but in only one instance did the line invade the macula. In

Table 4 Results: after cryotherapy

Patient	Eye	Preoperation	At last assessment		Visual function	Visual rating	Age (months)	Comments]
		Stage ROP†	Grade RLF‡					
				acuity§	field			
1	R	3+?	0	Good	Yes	2	6	D
	L	3+?	I	Good	Yes	2	6	
2	R	4+	II	Poor	Yes	1	86	CMA, MPE, N
	L	4+	II	Poor	Yes	1	86	CMA, MPE, N
3	R	3+b	I	20/40	Yes	2	87	CMA
	*L	3?	0	20/30	Yes	2	87	CMA
4	R	3+b	0	20/25	Yes	2	43	CMA
	L	3+b	0	20/25	Yes	2	43	CMA
5	R	4+	V	Blind	No	0	63	Angle closure at 42 months
	L	3+c	0	20/60	Yes	2	63	CHA, N
6	R	4+	III	<20/400	Yes	1	62	CMA, MPE, N
	L	3+c	I	20/400	Yes	1	62	CMA, MPE, N
7	R	3+c	II	Poor	Yes	1	10	MPE, OA, D
	L	3+c	II	Poor	Yes	1	10	MPE, OA
8	R	3+b	I	20/40	Yes	2	53	CMA
	L	3+b	0	20/30	Yes	2	53	CHA
9	R	4	0	Good	Yes	2	6	D
	L	3+b	0	Good	Yes	2	6	
10	R	4+	II	20/600	Yes	1	35	CMA, MPE, N
	L	4+	II	20/600	Yes	1	35	CMA, MPE, N
11	R	4+	II	<20/400	Yes	1	35	CMA, MPE, N, OA
	L	4+	II	<20/400	Yes	1	35	M, MPE, N, OA
12	R	4+	II	Good	Yes	2	29	CMA
	*L	3+?	V	Blind	No	0	29	Angle closure at 8 months
13	R	3+c	III	Poor	Yes	1	29	CMA, MPE, N, OA
	L	3+c	II	Poor	Yes	1	29	CMA, MPE, N, OA
14	R	3+b	I	Poor	Yes	1	23	CHA, MPE, N
	L	3+b	0	Good	Yes	2	23	CHA, N
15	*R	3b	0	Good	Yes	2	24	CMA
	L	3+b	II	Good	Yes	2	24	CMA
16	R	3+b	I	Good	Yes	2	20	CMA
	L	3+b	I	Good	Yes	2	20	CMA
17	*R	3b	0	Good	Yes	2	6	D
	L	3+c	0	Good	Yes	2	6	

* Eye not treated

† ROP = retinopathy of prematurity, ? = substage of ROP not determinable

‡ RLF = retrolental fibroplasia.

§ Good: 20/60 or better corrected acuity estimated, poor: less than 20/60 corrected acuity estimated

|| CHA = Compound hyperopic astigmatism, CMA = compound myopic astigmatism, D = deceased, H = hyperopia; M = myopia, MPE = macular pigment epitheliopathy; N = nystagmus, OA = optic atrophy

the right eye of patient 7 a new demarcation line (stage 1) appeared anterior to the cryotherapy and resolved spontaneously. One-half to one clock hour of stage 3+b retinopathy that had been missed between cryo spots usually resolved. However, if the disease progressed to stage 3+c it was treated.

The long-term results are shown in Table 4. 'Grade 0' retrolental fibroplasia has been used in the absence of cicatricial disease. Although these eyes had peripheral cryotherapy scars and posterior pole arterial tortuosity, the hallmark of past retinopathy, a grade of I seemed excessive.

A composite visual rating from 0 to 2 has been

devised. In Denmark it has been determined that children with less than 20/60 corrected acuity are visually disabled.²⁴ A rating of 2 means a corrected acuity of 20/60 or better with a functional field. A rating of 1 means a functional field with acuity less than 20/60, and a rating of 0 is a totally blind eye. When subjective evaluation of acuity was not possible, an estimate of visual function was made on the basis of morphological integrity of the posterior pole, central fixation, and the absence of nystagmus.

Macular pigment epitheliopathy and optic atrophy had an effect on visual acuity. Macular pigment epitheliopathy was present in all 13 eyes rated 1. The

serous effusion that can occur in eyes with severe retinopathy or a subtle serous detachment of the retina extending to the macula in stage 4 retinopathy may be primarily responsible for this epitheliopathy. Compression of these delicate eyes during treatment may have contributed to that macular pigment epitheliopathy. Its infrequency in those eyes treated with stage 3+b retinopathy is fairly reassuring. Optic atrophy was bilateral in all cases, and, in view of the other potential causes of optic atrophy in these infants, it is unlikely that it was caused by the application of cryotherapy. Nevertheless, prolonged compression of eyes during cryotherapy should be avoided.

ANALYSIS OF RESULTS

Tables 5 and 6 correlate the preoperative retinopathy of prematurity to the resulting retrolental fibroplasia and visual rating respectively.

From Table 5 the occurrence of grade II to V retrolental fibroplasia was significantly higher in stage 3+c treated group ($p=0.045^*$) and in the stage

4-4+ group ($p=0.006^*$) than in the stage 3+b group of eyes. A comparison of stage 3+c group with the stage 4-4+ group showed no significant difference ($p=0.147^*$).

From Table 6 the occurrence of visual disability (visual rating of 1 or 0) was significantly higher in the stage 3+c treated group ($p=0.013^*$) and in the stage 4-4+ group ($0.0005 < p < 0.005†$) than that which followed treatment of the stage 3+b group of eyes. Visual disability following treatment of the stage 3+c group compared with stage 4-4+ group was not significantly different ($0.3 < p < 0.4†$).

The above analysis indicates that treatment of stage 3+b retinopathy of prematurity by the methods outlined produces significantly less retrolental fibroplasia and significantly better visual function than treating stage 3+c or stage 4-4+ disease. In addition stage 3+c and stage 4-4+ retinopathy of prematurity are similar disease in terms of response to this treatment.

Discussion

There is a so far ill-defined critical mass of retinopathy of prematurity that will by natural progression result in loss of vision and significant retrolental fibroplasia. Any form of treatment, including its complications, must produce less visual disability and less RLF than the natural course of the disease.

The spontaneous resolution of stages 1 and 2 ROP without significant residual disease is most certainly the rule, and accordingly treatment of eyes reaching only these stages of disease is contraindicated. The success of treatment of selected cases of stage 3 disease or worse is affected by (1) the stage of ROP treated; (2) the method of treatment; (3) the location of treatment.

McCormick²⁵ has reported blindness and severe RLF in eyes that had any degree of retinal detachment or stage 4 ROP (12 of 14 eyes with grade V RLF and two with grade III RLF). Tasman²⁶ and Zak²⁷ have recently re-emphasised the significance of retinal detachment in ROP. McPherson *et al.*¹³ reported anatomical success with scleral buckling and cryotherapy in 75% of cases with stage 4 ROP. In this series, in which we treated early serous retinal detachments just posterior to the ridge with cryotherapy only to the ridge and the extraretinal fibrovascular proliferation at the ridge, anatomical success was achieved in 80%. However, only 20% escaped visual disability (corrected acuity of less than 20/60). Treatment of stage 4 ROP is clearly indicated but does not eliminate visual disability and RLF grade II or worse.

Treatment of stage 3 ROP was first reported by

Table 5 Anatomical results of treatment of 30 eyes with stage 3+ retinopathy or worse

Stage of ROP at treatment	Eyes	Grade of RLF after treatment					
		0	I	II	III	IV	V
3+?	n = 2	1	1				
3+b	n = 11	5	5	1			
3+c	n = 7	2	1	3	1		
4	n = 1	1					
4+	n = 9			7	1		1
Total	n = 30	9	7	11	2	0	1

? Could not determine substage from records

Table 6 Visual rating of 30 eyes after treatment for severe ROP

Worst stage of ROP treated	Eyes	Visual rating*			Comments†	
		2	1	0	MPE	OA
3+?†	n = 2	2				
3+b	n = 11	10	1		1	
3+c	n = 7	2	5		5	2 (2)
4	n = 1	1				
4+	n = 9	1	7	1	7	2
Total	n = 30	16	13	1	13	4 (2)

* Visual rating, 2 = corrected acuity $\geq 20/60$ plus functional field; 1 = corrected acuity $< 20/60$ plus functional field, 0 = totally blind eye

† ? = Substage of 3+ ROP indeterminable

‡ MPE = macular pigment epitheliopathy OA = optic atrophy.
() = suspected optic atrophy

Nagata *et al.*² using photocoagulation. Nagata² subsequently summarised 10 years of treatment. The borderline between avascular and vascular retina was the main target of photocoagulation. He stated that it did not seem essential to coagulate the proliferated vessels themselves. When present, a wide avascular area was also treated with random spots. Visual and anatomical (less than grade II RLF) success was accomplished in 95% of cases, but 21.8% of infants weighing 1500 g or less at birth were treated. He estimated that only 20% of those treated might have gone on to severe RLF if not treated. However, he also suggested that it may be reasonable to treat all cases which have any possibility of developing grade II RLF or worse.

Majima *et al.* treated with photocoagulation middle stage 3 in 12 eyes and watched the untreated fellow eyes.³ Two progressed to late stage 3 and were treated successfully. The remaining 10 resolved with RLF grade I.

Ben Sira *et al.*¹¹ treated 16% of eyes with any ROP in infants under 1500 g birth weight (32% of eyes with ROP in infants under 1000 g and 13% of eyes with ROP in infants from 1000 to 1500 g birth weight). They applied cryotherapy to the avascular retina without particular attempt to freeze the neovascular tufts. Fourteen of 18 eyes (78%) had RLF grade I or less. None were worse than grade II RLF. Their description of the ROP treated conforms to middle or moderate stage 3 ROP as in the International Classification and as qualified earlier in this report.

In this report 7.5% of all eyes with any ROP in infants under 1500 g birth weight were treated (12.5% in infants under 1000 g and 3.5% in infants 1000 to 1500 g birth weight). The eyes had middle or moderate stage 3 'plus' ROP or worse and the ridge extraretinal fibrovascular proliferative complex was treated with cryotherapy. No attempt was made to treat posterior extensions of extraretinal fibrovascular proliferation beyond the cryo spot that straddled the ridge. Of the middle stage 3 'plus' ROP treated eyes, 10 of 11 eyes (91%) had less than grade II RLF and no visual disability. The one visually disabled eye had grade II RLF. Of all the stage 3 'plus' eyes treated, 15 of 20 (75%) had less than grade II RLF and 14 of 20 (70%) had no visual disability. No eyes were completely blind, and only one eye had worse than grade II RLF.

We conclude that: (1) Treatment of ROP does reduce RLF and visual disability. (2) Stage 4 ROP is a clear indication for treatment; scleral buckling and cryotherapy are probably necessary for advanced detachments; cryotherapy alone may succeed with early detachments just posterior to the ridge. (3) Late or severe stage 3 ROP can be treated with cryotherapy or photocoagulation, but the elimination of

visual disability and ocular morbidity is unlikely. (4) The treatment of selected progressive cases of middle or moderate stage 3 'plus' ROP can achieve the goals of therapy. It must be emphasised that only selected progressive cases of stage 3 'plus' ROP should be treated, with 'plus' disease being the major criterion for selection. (5) Several methods of treatment and locations of treatment appear to be effective.

Accordingly our attention should be directed to the improvement of diagnostic methods and documentation and to the comparison of methods and locations of treatment. In addition it is fundamental that the International Classification of Retinopathy of Prematurity be adopted as the sole standard of communication to enable critical analysis and peer review.

* Fisher's exact test

† χ^2 with 2 degrees of freedom

A W Rademaker, PhD, Department of Community Health Science, Faculty of Medicine, University of Calgary, did the statistical analysis

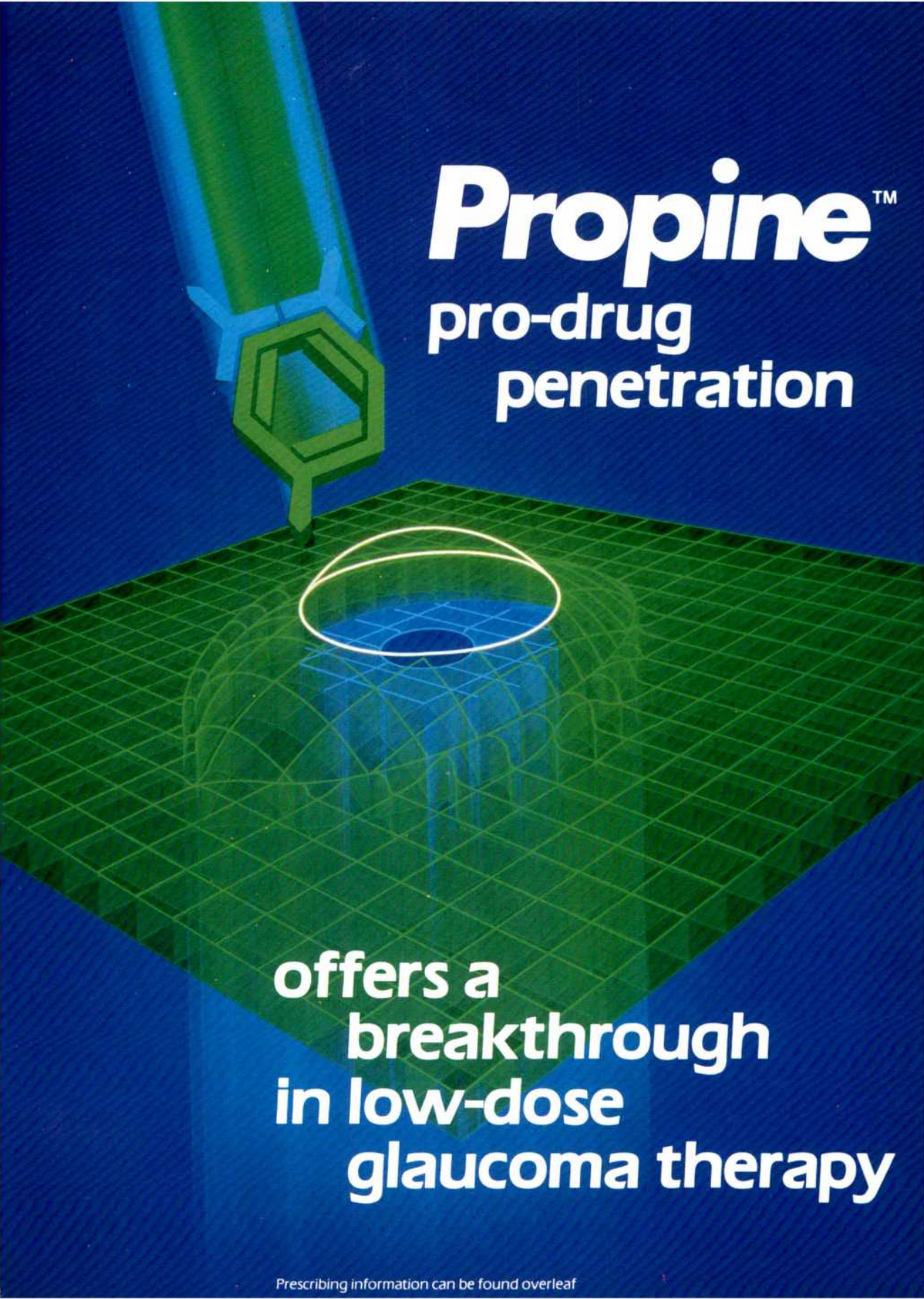
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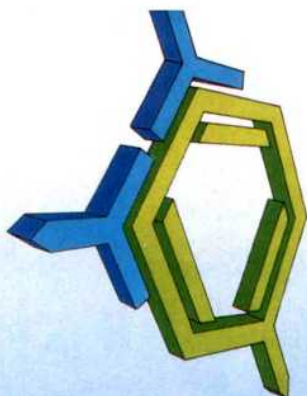


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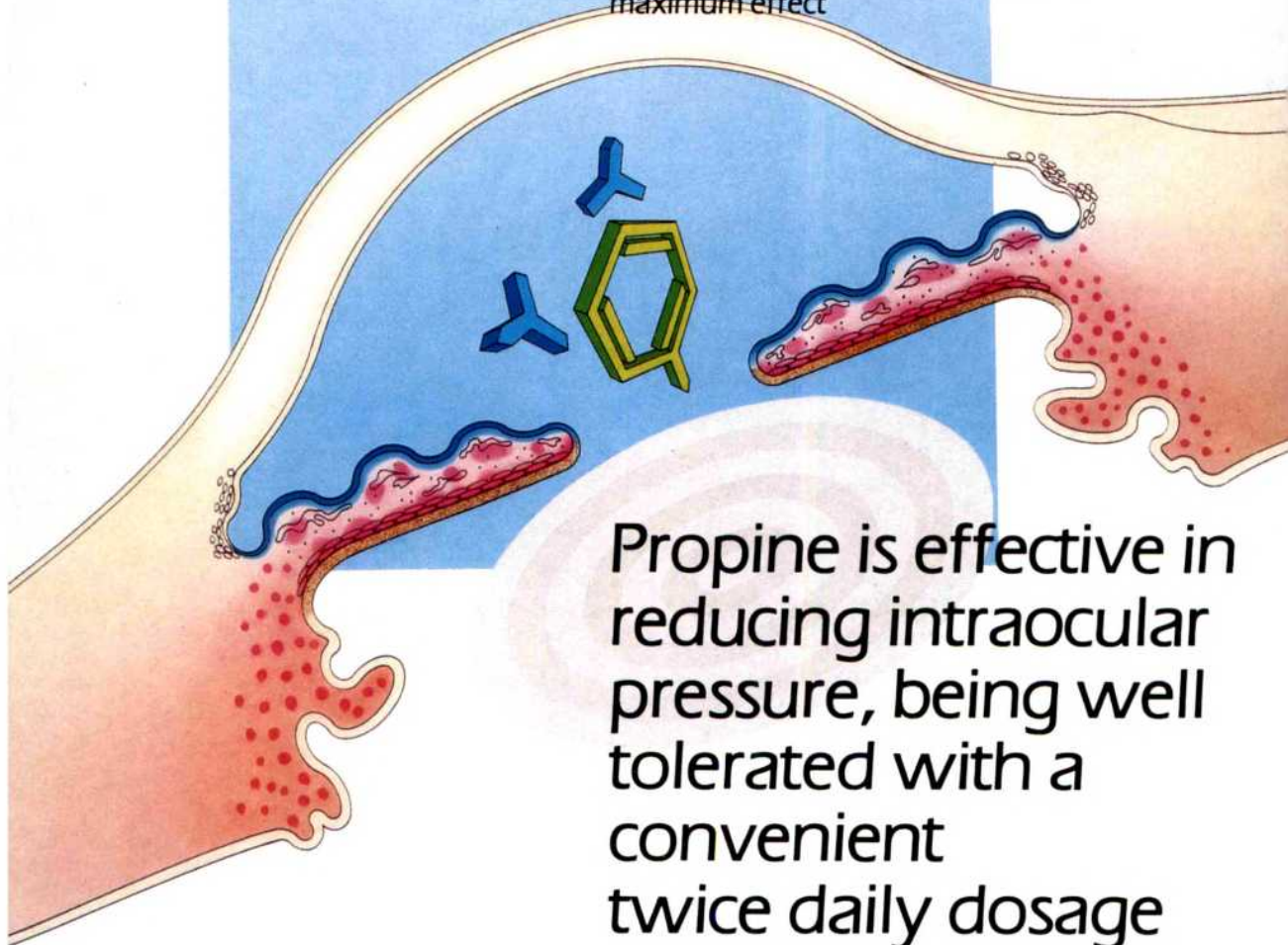
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Improvement of photostress recovery testing after extracranial-intracranial bypass surgery

BARRETT KATZ AND PHILLIP R WEINSTEIN

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SUMMARY A patient with carotid occlusive disease experienced episodes of light-induced amaurosis in an eye with changes of venous stasis retinopathy. Though his macula appeared normal on examination, the macular photostress test (MPST) was prolonged. After anastomosis of a superficial temporal artery with the middle cerebral artery his symptoms resolved and his MPST returned to normal. The MPST may serve as a diagnostic stress test for the retinal circulation in cases of carotid disease.

The macular photostress test (MPST) monitors in a semiquantitative fashion the effect of light on the retina. The test depends on a subject's ability to discern the resolution of a photic-induced scotoma. It has been shown to be a valuable adjunct in differentiating subtle maculopathy and subclinical optic neuropathy, and has prognostic value in predicting recovery or progression of macular disease.¹

In this test the macula is dazzled with a hand-held penlight, and the time required for subjectively measured visual acuity to return to prestress levels is compared with normal recovery times. Best corrected acuity for distance is determined. With one eye shielded the patient looks directly into a hand-held muscle light for 10 seconds as that light is held 3 cm from the eye. Immediately after the light is removed the patient is asked to read test letters one line larger than his best acuity. Photostress recovery is recorded in seconds, with the end point being the capacity to read any three letters of that predetermined line. The procedure is then repeated for the opposite eye.

We report experience with a patient whose clinical course and test results suggest the use of the MPST in evaluating patients with carotid occlusive disease.

Case report

A 60-year-old right-handed native-born white male had been followed up for angiographically confirmed

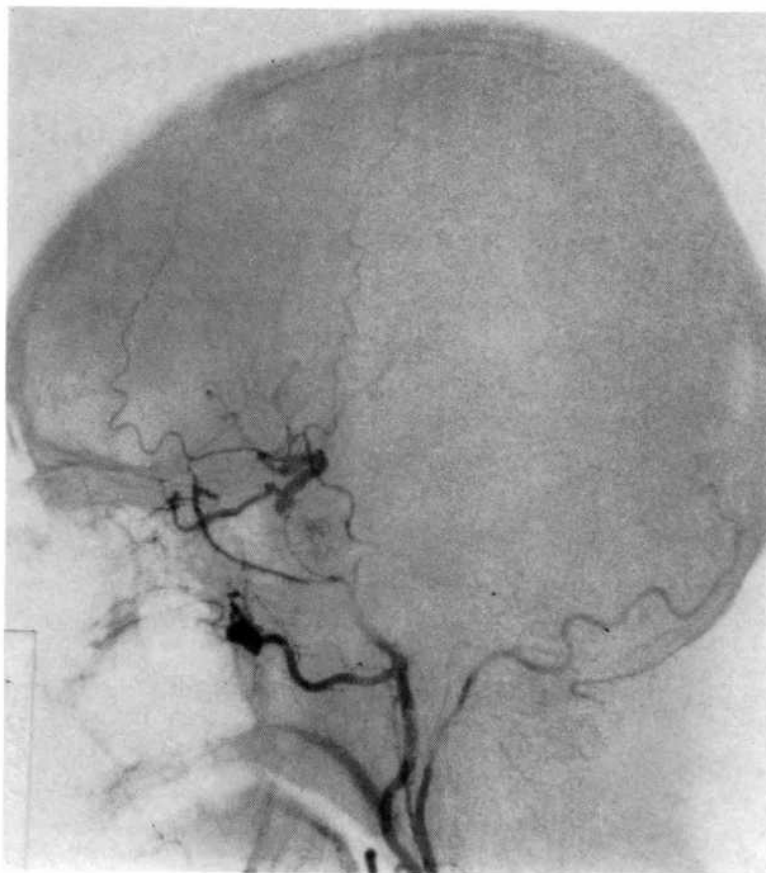
atherosclerotic coronary vascular disease. He was not hypertensive or diabetic, and was successfully managed on propranolol and nitroglycerin. In November 1982 he noted transient loss of vision in his left eye precipitated by bright light or mild exercise. Episodes occurred daily and were characterised by diminution of central vision with relative preservation of peripheral vision. They were occasionally accompanied by phosphenes and persisted for 3-5 minutes. His visual loss was not accompanied by any other neurological or neuro-ophthalmic symptoms, and it resolved without sequelae.

In December 1982 he suffered more classical amaurosis of the left eye, accompanied by aphasia. He was admitted to hospital and studied angiographically. His aortic arch showed generalised atherosclerotic irregularity and tortuosity, as did the proximal brachiocephalic vessels. There was a large ulcerated plaque in the region of the right common carotid bifurcation associated with haemodynamically significant stenosis of the proximal parts of the right internal and external carotid arteries. A sacular aneurysm was noted in the region of the anterior communicating artery, and slight atherosclerotic irregularity was present in the right carotid siphon. The left internal carotid artery appeared to be completely occluded at its origin. There was reconstitution of the carotid siphon on the left side via collaterals through the ophthalmic artery, which was hypertrophied (Fig. 1). The external carotid artery showed minimal stenosis proximally.

A left internal carotid endarterectomy was performed with removal of thrombus but unsuccessful

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Fig. 1 Left common carotid arteriogram shown in the lateral projection demonstrates occlusion of the proximal internal carotid artery (ICA) with retrograde flow through an enlarged ophthalmic artery filling the intracranial ICA and its branches.



establishment of back flow. A tight stenosis at the take-off of the left external carotid was observed, and a distal common and external carotid endarterectomy was performed.

Two weeks later his right carotid artery was explored. At operation a tight stenosis of both internal and external carotid arteries was identified, and a plaque was removed from the area of bifurcation. The operation was without complication or sequelae.

Postoperatively there was a decrease in frequency of his light-induced amaurosis and total disappearance of his classical amaurosis fugax. Over the ensuing months no symptoms of hemisphere ischaemia developed. When his light-induced amaurosis increased in frequency, he was referred to us for further examination.

When he was first seen in June 1982 he had small blot haemorrhages and microaneurysms in the midperiphery of his left eye only, accompanied by darkening and mild dilatation of the venous retinal vasculature. The results of macular examination

were normal in both eyes (Figs. 2, 3). Fundus fluorescein angiography showed punctate areas of capillary dilatation associated with dot and blot haemorrhages and microaneurysmal formation in the midperiphery of the left eye (Fig. 4). The right eye was ophthalmoscopically and angiographically normal. Ophthalmodynamometry revealed a diastolic reading of 30 scale units on the right and less than 5 scale units on the left. Because of the history of light-induced amaurosis, photostress testing was performed according to the technique of Glaser *et al.*¹ The right macula recovered function in 10 seconds while the left macula required 80 seconds for recovery. Cerebral blood flow (CBF) measurement after intravenous administration of Xenon-133 showed a blood flow of 36 ml/min/100 g in the left hemisphere and flow of 51 ml/min/100 g in the right hemisphere.

To decrease the retinal ischaemia and to increase flow to the hemisphere an anastomosis was performed between a left superficial temporal artery and the middle cerebral artery (STA-MCA). Post-



Fig. 2 Fundus photograph of posterior pole of the right eye showing normal anatomy.

operatively the patient was entirely free of transient visual loss. Repeat neuro-ophthalmic examination 10 days after surgery revealed no change in the appearance of his left retina. The MPST, however, returned to normal, with a recovery time of less than 10 seconds in that eye. Ophthalmodynamometry still

suggested decreased flow in the left central retinal artery.

Four months later the patient remained free of visual symptoms. He underwent follow-up intra-venous digital angiography, which revealed patency of the STA-MCA anastomosis. His retinal examination was unchanged, and his MPST remained normal bilaterally.

Discussion

Venous stasis retinopathy describes the chronic retinal changes of ischaemia due to haemodynamically significant reduction of flow through the internal carotid artery.² It is characterised by small retinal haemorrhages, microaneurysms, and focal areas of capillary dilatation. It includes dilatation, darkening, and tortuosity of the venous side of the retinal circulation and has an anatomical predilection for the midperiphery. The diagnosis is made in the setting of severe chronic occlusive carotid disease, and recognised by the finding of abnormally low central retinal artery pressure on ophthalmodynamometry. Resolution of this retinopathy has been reported after endarterectomy³ and after STA-MCA bypass surgery.^{4,7}

In 1979 Furlan *et al.*⁸ described five patients with carotid artery occlusive disease and monocular transient visual loss precipitated by bright sunlight. These patients showed angiographic evidence of high-graded stenosis or occlusion of the ipsilateral carotid



Fig. 3 Fundus photograph of posterior pole of the left eye illustrates darkening and mild dilatation of the venous vasculature.

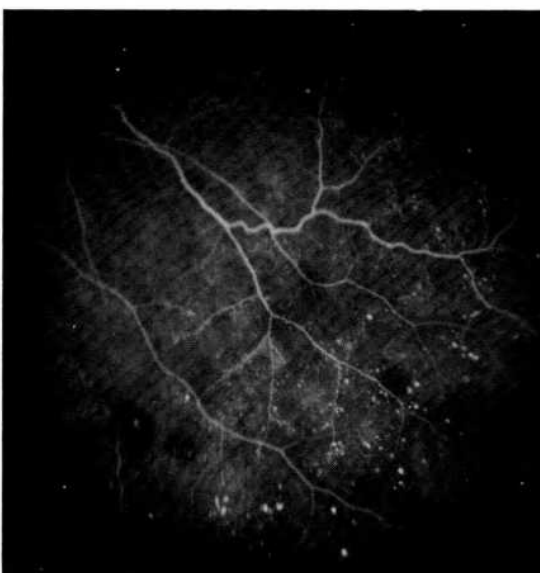


Fig. 4 Fluorescein angiogram of the left fundus illustrates blot haemorrhages and microaneurysms in the midperiphery.

artery. The authors concluded that such visual loss in patients with severe carotid occlusive disease occurs on the basis of local haemodynamic insufficiency rather than emboli. A recent report affords objective documentation of such light-induced amaurosis by recording an attenuated visually evoked response in the two-minute interval following exposure to light.⁹

Our patient had light-induced amaurosis associated with mild venous stasis retinopathy. He had angiographically confirmed ipsilateral internal carotid artery occlusion, and his left hemisphere was perfused in a retrograde fashion through his ophthalmic artery. Preoperative examination revealed a lower retinal artery pressure as determined by ophthalmodynamometry and prolonged photostress recovery time. He underwent successful STA-MCA bypass surgery, which was followed by the disappearance of his light-induced monocular blackouts and the return of his photostress test results to normal. These changes occurred without any discernible regression of his venous stasis retinopathy or change in retinal artery pressure, suggesting the MPST may be a sensitive and early sign of improved retinal perfusion.

The MPST is primarily a test of macular function,^{10,11} if only because of the parameter we use to measure it—macular vision. Recovery from photostress is presumed to be a function of the rate of visual pigment bleaching and resynthesis and dependent on the relation between the retinal pigment epithelium, Mueller cells, and photoreceptors (that is, outer retinal function). We postulate that our patient's photic-induced amaurosis and prolonged photostress test were a manifestation of outer retinal ischaemia secondary to carotid insufficiency. Another possibility is a light-induced photoregulatory change in the inner retinal circulation. In light, more choroidal oxygen diffuses into the inner retina than in the dark. The autoregulatory response of the retinal vasculature to increased local tissue oxygen results in decreased blood flow in the light.¹² Perhaps in the ischaemic eye the light-induced increased inner retinal oxygen from the choroid drives the vasculature toward vasoconstriction. In either case exposure to light caused further reduction of blood flow to a borderline compensated inner and outer retinal circulation, precipitating light-induced amaurosis.

Abnormal photostress testing has been commonly recognised in macular degeneration, central serous choroidopathy, and disease of the retinal pigment

epithelium. We believe the MPST may in selected cases serve as a diagnostic stress test for the autoregulatory capacity of the eye. Deviation from the norm may be a sign of underlying carotid insufficiency.

The improvement of the photostress test results after STA-MCA anastomosis parallels previous reports of the resolution of venous stasis retinopathy and elimination of light-induced amaurosis following extracranial bypass surgery. Although the anastomosis is placed on a cortical branch of the middle cerebral artery at some distance from the carotid origin of the ophthalmic artery, it is postulated that augmentation of collateral flow to the hemisphere through the bypass reduces the 'steal' from the ophthalmic circulation and results in improved blood flow to the eye.

The authors gratefully acknowledge the thoughtful reviews and suggestions of Drs William F Hoyt and John J Weiter.

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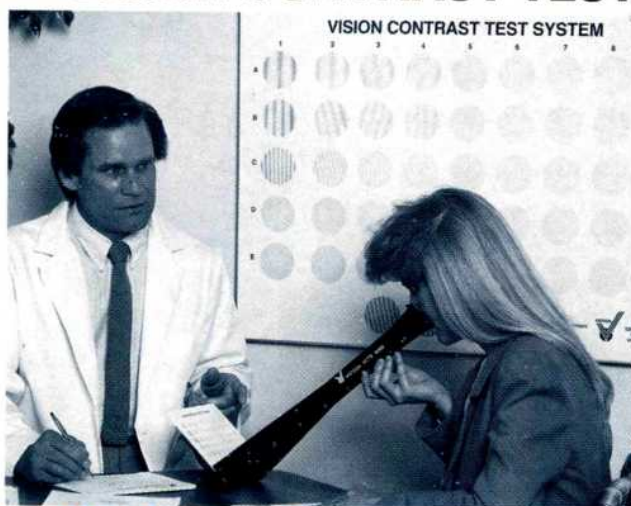
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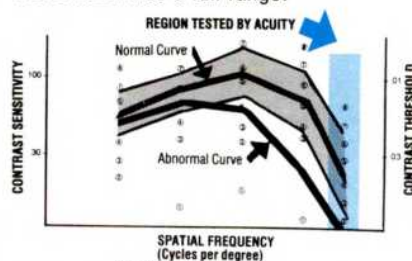
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Delayed-onset chloroquine retinopathy

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SUMMARY Delayed-onset chloroquine retinopathy was diagnosed in a patient seven years after cessation of treatment by a total dose of 730 g of chloroquine for rheumatoid arthritis. Visual functions continued to deteriorate after the diagnosis. Periodic examinations by ophthalmoscopy and by functional tests such as EOG and visual fields should be continued in patients at risk of delayed-onset chloroquine retinopathy after discontinuance of the drug.

Chloroquine and hydroxychloroquine have been used in the treatment of rheumatoid arthritis and discoid and systemic lupus erythematosus since the early 1950s. Towards the end of the same decade serious ocular complications became apparent. Corneal deposits due to chloroquine were first noted in 1958.¹ A retinopathy with visual loss was confirmed by Hobbs *et al.*² and Sternberg *et al.*³ in 1959. Similar observations with hydroxychloroquine were subsequently reported, and this entity became well documented over the years.

The retinal findings are usually bilateral and vary from mild non-specific changes consisting of fine pigment mottling of the macula with loss of foveal reflex to the characteristic pattern described as the 'bull's eye' lesion with granular hyperpigmentation of the perifoveal area surrounded by a concentric zone of depigmentation which is encircled by another ring of pigment.⁴ In advanced cases attenuated retinal arterioles, pallor of the optic disc, and a generalised pigmentary retinal disturbance resembling retinitis pigmentosa were described.

Several factors have been reported to predispose the retina to the development of chloroquine toxicity. These are daily dosage, duration of treatment, serum drug level, age of patient, and specific drug used.^{5,6} However, a review of the literature suggests that the daily dosage is the most important risk factor. Recommendations by Mackenzie⁷ limit the daily dosage to 3.5 to 4.0 mg/kg of chloroquine or 6.0 to 6.5 mg/kg of hydroxychloroquine, based on lean body weight. The patient should be subjected to an annual ocular examination and biennial if he is 65 years old or more. Treatment should be adjusted for

pharmacokinetic variables such as renal failure. Adherence to these safety rules should reduce the retinopathy to a minimum and prevent loss of vision.

We present a case of severe advanced chloroquine retinopathy which began seven years after discontinuation of the drug. Delayed onset chloroquine retinopathy, the proper term for such a condition, is little known, poorly understood, and only a few reports of it exist.

Case report

A 50-year-old woman had been under our care since 1965, when she was diagnosed as having seropositive rheumatoid arthritis. Cryotherapy failed because of a severe rash, and she was started on chloroquine tab. 250 mg once daily in 1966. She was treated with the same dosage for the following eight years, with a good response. Throughout the years tests of visual acuity and ophthalmoscopy were performed at regular intervals and were found to be within normal limits. In 1974 chloroquine therapy had been discontinued because of a possible drug-related polyneuropathy, with symptoms of muscle weakness and wasting. Electromyography (EMG) showed loss of motor units, fibrillations, and impaired conduction. Visual acuity tests and the fundi were normal. As the disease had been under control, with only mild arthralgia, the patient was put on brufen (Motrin) tab. 400 mg twice daily. She continued with this treatment for the next six years. In total she was treated with 730 g of chloroquine. In late 1982, almost seven years after discontinuation of the chloroquine therapy, she started to complain for the first time of visual disturbances.

The patient was referred to the eye clinic and presented with difficulty in reading. The visual acuity

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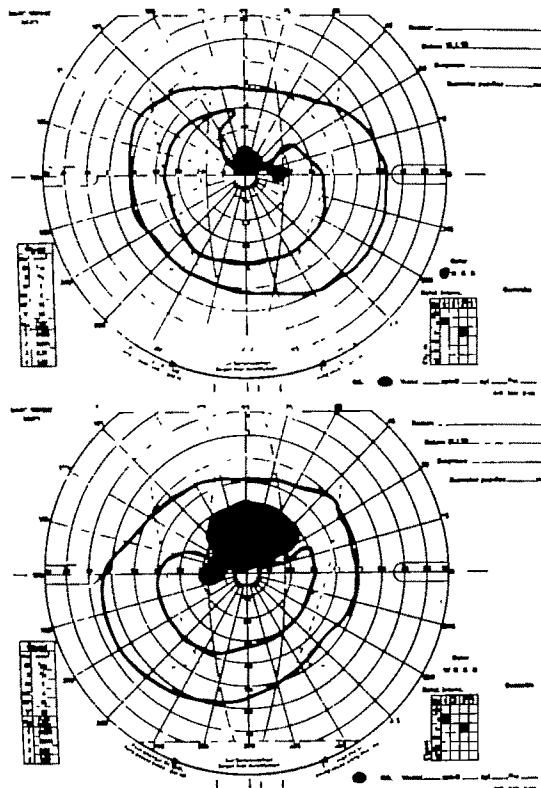


Fig. 1 Visual fields 10 years after cessation of chloroquine treatment, showing a large scotoma in the upper part of the visual field.

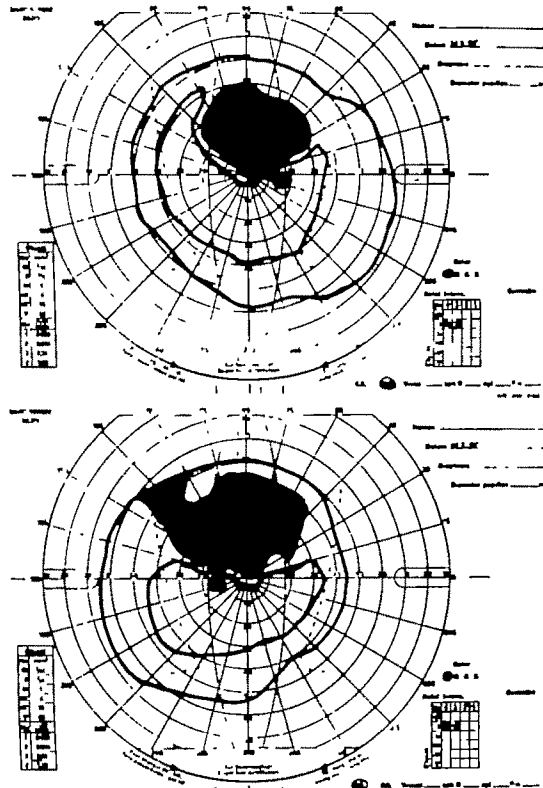


Fig. 2 Visual fields 11 years after cessation of chloroquine treatment, showing further increase in the size of the scotoma.

was 20/60 in the right eye with best correction, and 20/60 in the left eye improved with correction to 20/40. The anterior segment was normal. The fundus examination revealed the typical bull's eye appearance of chloroquine retinopathy in both eyes.

On colour testing the patient could not recognise any of the American optical Hardy-Rand-Rittler (A-O HRR) colour testing plates. The visual field examination showed paracentral scotoma in both eyes.

The electro-oculogram (EOG) was disturbed. The Arden ratio was 1.65 in the RE and 1.9 in the LE. The electroretinogram (ERG) was abnormal, and decreased amplitudes of a waves (40–50 μ V) and b waves (160–190 μ V) were noted.

On follow-up examination at the eye clinic three years after the onset of symptoms the patient's visual acuity was unchanged, but a deterioration in the visual field with enlargement of a relative paracentral scotoma was found. This was unnoticed by the patient, because it was confined to the upper visual field (Figs. 1, 2).

The EOG results, which in 1981 were 165% in RE and 190% in LE, varied in the four years of follow-up from 120% to 140% in both eyes.

Discussion

Progression of visual loss after cessation of treatment by chloroquine or hydroxychloroquine has been reported in single case reports over the years. The interval between the last dosage of the drug and the development of retinopathy ranged from 1 year to 10 years.¹¹ Scherbel *et al.*⁴ and Okun *et al.*¹⁰ reported cases in which the onset of a pigmentary retinopathy started 18 and 33 months after chloroquine therapy had been discontinued.

Some cases have progressed to extreme deterioration of vision. Burns described two cases of delayed onset chloroquine retinopathy at two to four years and at five years after discontinuation of chloroquine.¹¹ Carr and co-workers reported a five-year follow-up of 10 patients after discontinuation of therapy. The majority of their patients with chloro-

quine retinopathy remained stable. A few patients in the early stages of retinopathy returned to normal, whereas some showed progressive maculopathy.¹² Similar observations are shared by Brinkley *et al.*, who followed up seven patients for a period of 10 years after discontinuation of the treatment.¹³ Our patient had a lag period of seven years between discontinuation of chloroquine and the onset of visual disturbances.

During the course of her treatment with chloroquine she had regular ophthalmoscopy and visual acuity examinations done, which were all within normal limits. Electrophysiological examinations were not available at that time. The patient consumed an approximate total dose of 730 g during the eight years of treatment with chloroquine. Rarely, ingestion of 100 g of chloroquine may cause a retinopathy. The risk becomes significant when the total dosage exceeds 300 g.¹⁴ Nylander reported a 50% increase of retinopathy in patients receiving a cumulative dose which exceeds 900 g of chloroquine.¹⁵ Ogawa *et al.* recently reported a survey on 68 chloroquine retinopathy patients who had instituted a lawsuit against chloroquine manufacturers.¹⁶ The total dosage per patient ranged from 45 to 674 g (mean 274 g) and the duration of therapy from 16 to 129 months (mean 51 months). All patients had visual field defects and none showed improvement. On the contrary, progression was noted in 10 patients after discontinuation of chloroquine therapy. In five of these cases the progressive impairment continued for more than five years after chloroquine therapy was stopped.

The pathogenesis of the retinopathy related to chloroquine is not fully known. Histological examinations show evidence of destruction of rods and cones and migration of pigment clumps.¹⁷ Antimalarial compounds are known to bind to melanin, and chloroquine has been shown to be deposited in the melanin-containing tissues of the eye (the iris, choroid, and pigment epithelium of the retina) in concentrations many times in excess of those in other body tissues.^{10,18} It has also been shown that small amounts of antimalarial drugs may be recovered from the urine even years after their discontinuation, mainly owing to slow release of the residue bound to melanin.¹⁹ It has therefore been suggested that this binding to the melanin may be related to the toxicity,¹⁷ and it is postulated that the high affinity for the melanotic tissues may cause the delayed onset of the retinal toxicity to the drug.

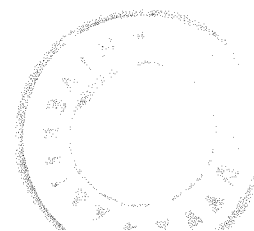
Though delayed onset of chloroquine retinopathy is rare, we wish to emphasise its severity and suggest the need for follow-up by functional tests such as those of the visual fields and EOG. They should probably be done on all patients who have received 300 g of chloroquine or more. There is no other way to know which patient is liable to suffer from delayed-onset chloroquine retinopathy.

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Fluorescein angiography of the iris in anterior segment pigment dispersal syndrome

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SUMMARY The results are presented of fluorescein angiography of the iris in 11 patients with anterior segment pigment dispersal syndrome. These show a general hypovascularity of the iris with fine neovascularisation at the pupil margin and the peripupillary area. Hypoplasia of the iris stroma was also present in many cases. When the condition was virtually unilateral, the vascular changes were present though less marked in the relatively unaffected eye. It is postulated that the anterior segment pigment dispersal syndrome is secondary to a congenital mesodermal deficiency of the iris stroma with hypovascularity of the iris, which forms a poor support tissue for the pigment epithelium of the iris, resulting in shedding of pigment granules particularly in the region of the attachment of the dilator muscle to the pigment epithelium. The condition may be hereditary. Because of the hypovascularity the mesodermal hypoplasia may be progressive, but pigment release may diminish in later life with treatment, with consequent diminution of pupil activity.

The cause of the release of pigment granules from the pigment epithelium of the iris in the anterior segment pigment dispersal syndrome is of interest, as it is generally accepted that the deposition of the granules in the drainage angle causes the pigmentary glaucoma which usually accompanies this syndrome. The condition was considered by Perkins and Jay,¹ who drew attention to the numerous iris processes commonly seen in pigmentary glaucoma, which they considered to be due to a developmental defect of the outflow channels, with the deposition of pigment possibly contributing to obstruction of aqueous outflow but not being the primary cause.

Fine *et al.*² thought pigmentary glaucoma to be a developmental defect with idiopathic dysplasia of the iris epithelium and a distinct condition from chronic simple glaucoma. Kupfer *et al.*³ considered it to be a congenital or developmental abnormality especially affecting the inner and outer epithelial layers of the iris. Campbell⁴ considered the pigment release to be due to mechanical factors as the iris rubbed against the anterior packets of the ciliary zonules especially in myopic eyes.

In a prescient paper Lichter⁵ thought that an iris stromal defect, possibly vascular, may be the link

between the abnormalities of the drainage angle commonly seen in pigmentary glaucoma and the defects in the pigment epithelium of the iris. Olander *et al.*⁶ considered a possible genetic origin, while Scheie and Cameron⁷ considered a multifactorial inheritance pattern. Chew and Deutman⁸ reported one case of pigment dispersal syndrome and pigmented pattern dystrophy of the retinal pigment epithelium, though a recent series⁹ of cases of pigmentary glaucoma showed no association with disorders of the pigment epithelium elsewhere in the eye.

To elucidate further the cause of the pigment release in this condition we have carried out iris fluorescein angiography on a number of cases, correlating the results with the clinical findings. This study has led us to the conclusion that anterior segment pigment dispersal syndrome is caused by a fault in the mesodermal support tissue to the iris and in particular a relative deficiency of the iris vasculature.

Material and methods

Fluorescein angiography of the iris was carried out on 11 patients with pigment dispersal syndrome. A Zeiss fundus camera was used as the light source, and a

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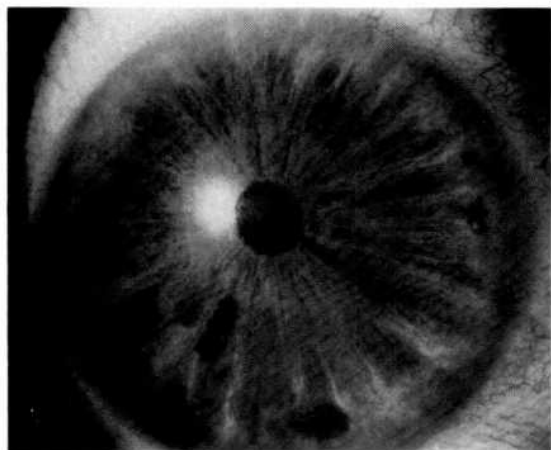


Fig. 1a Right eye of 55-year-old female, brown iris, showing the general thinning of the iris stroma, with a very open structure giving the appearance of a loose sponge work, the pigment epithelium being visible through the interstices of the stroma. The pupil is constricted by miotic drops.

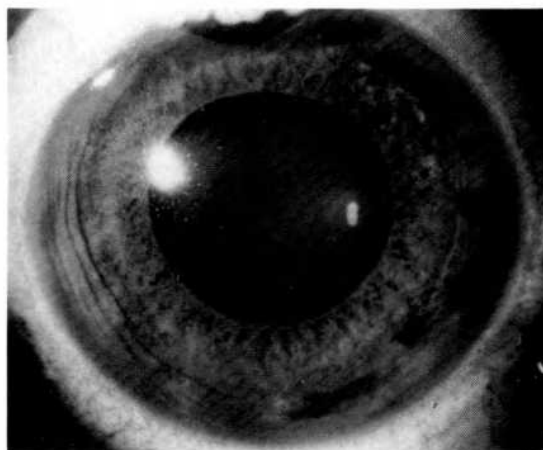


Fig. 1b Left eye of same patient as in Fig. 1a with similarly open stromal meshwork. The eye has previously had a drainage operation and the pupil is mobile and semidilated, though no drops are being used.

Nikon F3 camera was used to take the photographs with a 105 mm Macro lens, a PN -1 tube, and CU close-up lenses. The F stop was f5.6 for the first and f8 for the second run. The fluorescein dosage was 5 ml 25% for the first run and 3 ml 25% for the second run. Tri-X film was processed with Microdol X stock solution developed at 22°C for 14 minutes to obtain the negatives.

On gonioscopy all these patients had a heavy deposition of pigment in the trabecular tissue of the drainage angle. In addition to this there was other evidence of pigment dispersal, namely, reflux of light through the pigment epithelium of the iris in all cases, Krukenberg spindles in all cases, and pigment deposition at the attachment of the zonule to the lens in five cases.

Corneal endothelial cell counts were carried out on six patients, and all cases were examined with the slit-lamp for diffuse atrophy or hypoplasia of the iris stroma. This was assessed on thinning and loss of the normal structure of the iris stroma, so that the normal radial structure of the iris was less apparent, and it was possible to see some detail of the pigment epithelium through the thinned stroma.

The patients comprised seven males and four females aged 26 to 73, average age 48.7 years, range 26-73, SD 12.1 years. Most had light coloured irides, only two having a brown iris. Three patients were under the age of 40 and seven were under 50.

Results

Evidence of atrophy of the iris stroma was found on

biomicroscopy in six patients. It consisted of loss of the normal iris architecture and a thinning of the iris stroma so that the pigment epithelium could be seen easily through the stroma. These patients often had semidilated pupils which did not contract fully with miotics, perhaps owing to a general loss of iris tissue and an effect on the iris sphincter muscle. (Figs. 1, 2).

In four patients the pigment dispersal was much more marked in one eye than the other, in which it seemed slight though present to a limited degree. One such patient had normal intraocular pressure in each eye. In the other three the more affected eye

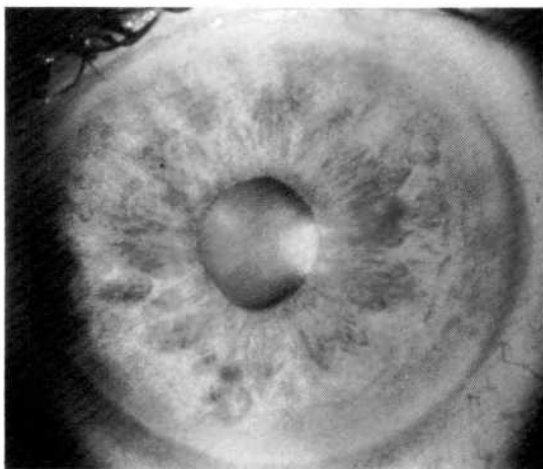


Fig. 2 Right eye of a 73-year-old male, light grey iris with pigment deposition in the stroma, which shows diffuse atrophy. The pupil is not completely miotic in spite of strong miotic drops.

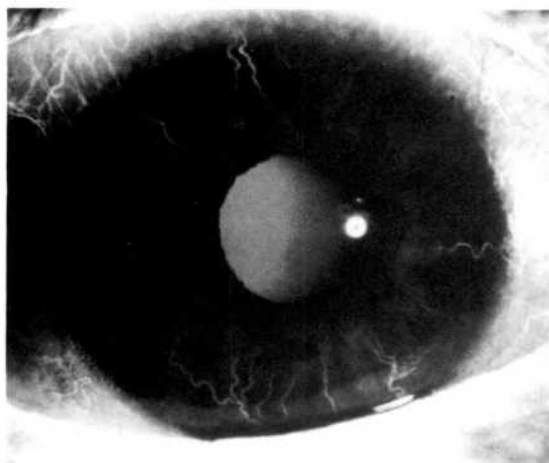


Fig. 3a Right eye of a 58-year-old male at 25.7 seconds; arterial phase has just begun. Note extreme paucity of vessels in the upper and temporal quadrants of the iris.

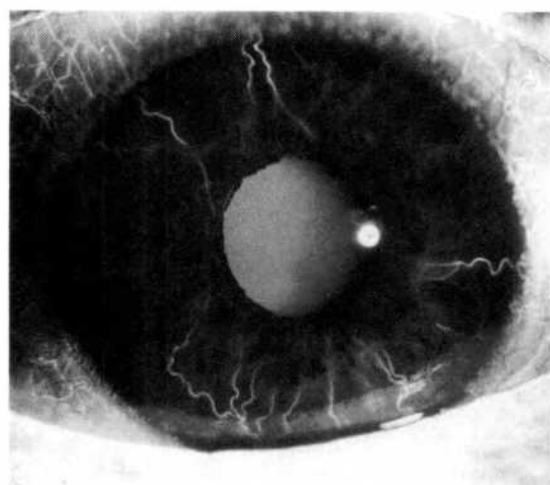


Fig. 3b Same eye at 28.9 seconds; the arterial phase is well established and the lack of arterioles previously noted persists.

had the higher pressure, the fellow eyes being within normal limits.

On iris angiography all eyes showed vascular hypoperfusion of the iris with scant, attenuated iris vessels. In four eyes no radial arteriole was seen in one quadrant of the iris or only one to three arterioles were present to supply adjoining quadrants (Figs. 3a-e). In all the other eyes the number of arteries was greatly reduced and their calibre attenuated (Figs. 4, 5). Appearance of the dye in the arterioles was at an average of 25 seconds (range 21–32 s, SD 2.3 s). Appearance of dye in the veins seemed to be delayed for an average of 10.1 seconds later (range 7–15 s, SD 2.3 s).

All eyes showed leakage of dye from fine peripupillary neovascularisation, with leaks also occurring from neovascular tufts at the pupil margin. This leakage from peripupillary vessels and from the pupil margin was copious in late pictures, strongly suggesting that this was neovascularisation and not merely the unmasking of a normal capillary network by the iris atrophy (Figs. 3e, 3f).

All but two patients showed aberrant vessels and loops in the peripheral iris stroma, with some leak from neovascular tufts in the peripheral stroma. These findings were present in both the younger and the older patients. The two patients with a brown iris showed findings similar to but less marked than those

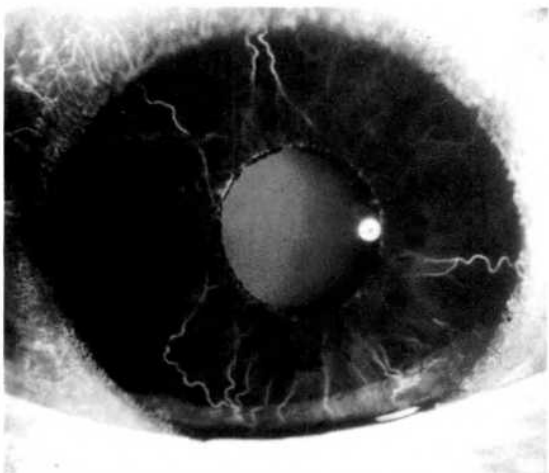


Fig. 3c Dye has now reached tufts at the pupil margin. Arterial phase at 32.2 seconds.

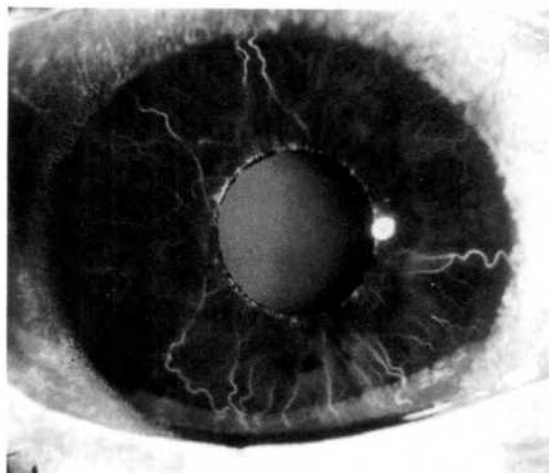


Fig. 3d At 34.8 seconds the venous phase is just beginning, and some leak is occurring at the pupil margin.

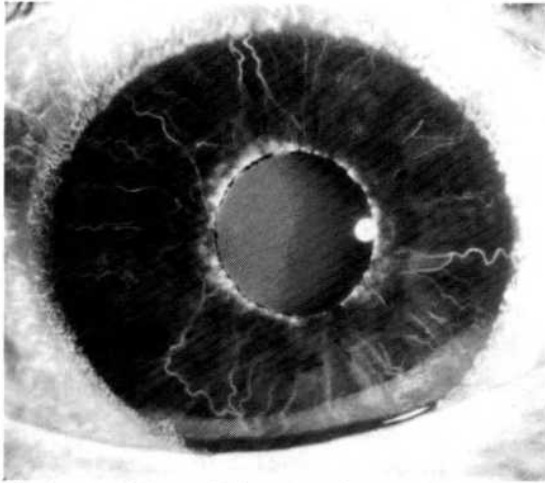


Fig. 3e At 43.7 seconds the venous phase is well established, and there is considerable leak from the pupil margin.

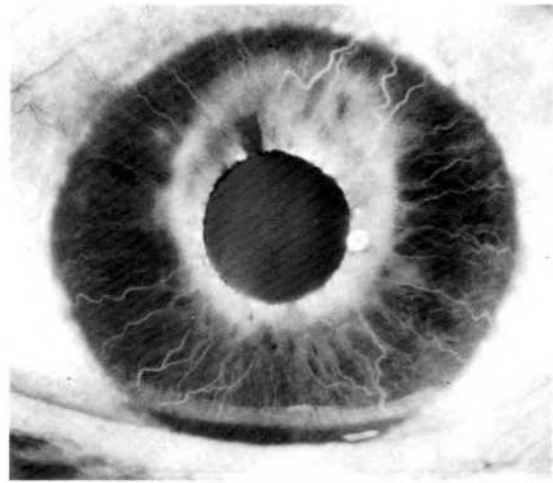


Fig. 3f The left eye of the same patient at 58.5 seconds in the second run. This fellow eye showed little evidence of pigment dispersal, but there was relative hypoperfusion of the iris, and a late heavy leakage of dye from pupillary and peripupillary vessels is evident with a 'smoke stack' effect.

with a blue iris, the masking of the vascular pattern which occurs with a brown iris being diminished by the iris atrophy (Figs. 4a, 4b). In the four patients in whom pigment dispersal was more marked in one eye than in the fellow eye the findings on iris angiography were similar to those from the other eyes in the group. Though they were less marked in the less affected eye in these patients, the vascular changes were still present (Figs. 3a-f).

Corneal endothelial cell counts were performed on six of the patients and ranged from 2000 to 2675 cells/mm² with some pleomorphism in three patients,

suggesting some interference with endothelial cell function in these unoperated eyes.

Discussion

The normal iris angiogram^{10,11} shows radially running arterioles which course from the iris root towards the pupil, tapering a little in calibre and following a slightly tortuous course. Few collateral branches are given off, and near the pupil the arterioles break up

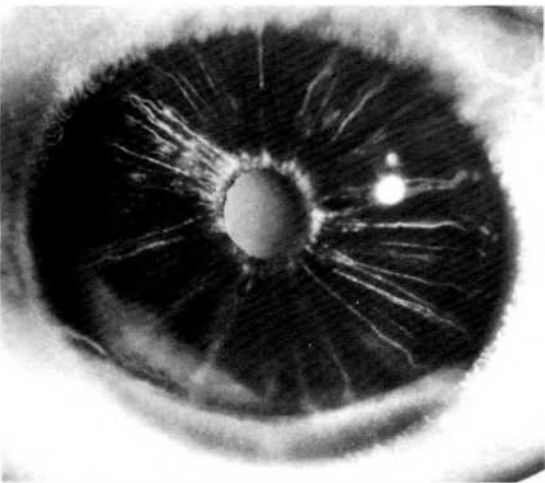


Fig. 4a Iris angiography at 42.2 s of same eye as in Fig. 1a, showing relatively sparse iris radial vessels with early pupillary and peripupillary neovascularisation.



Fig. 4b The same patient at 71.8 showing much heavier leakage from the pupillary and peripupillary neovascularisation. There is also some leakage of dye in the more peripheral iris stroma.

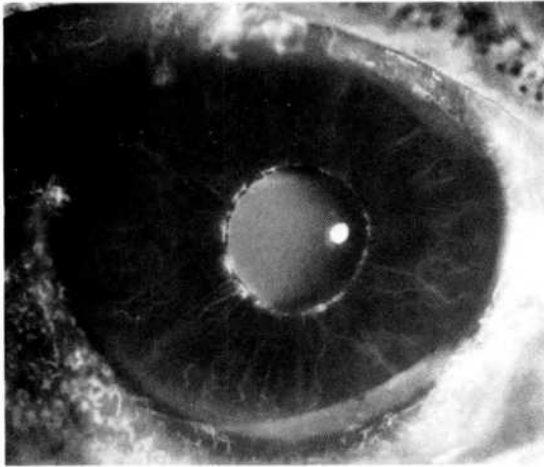


Fig. 5 Iris angiography at 61.5 s of same patient as in Fig. 2, showing the poor and attenuated vasculature with leaking neovascularisation in the pupillary and peripupillary area.

into fine vessels which interlace to form a fine peripupillary network, and arteriovenous bridges may be seen at the pupil border. The arterioles are evenly distributed in all the quadrants of the iris. Veins run a similar radial course, are more numerous and deeper. The arterioles fill 9–20 or more seconds after dye is injected in the arm and the veins fill about 4 seconds after the arterioles. No leakage is seen in young patients, but some patients over the age of 50 will show small tufts of fluorescein leakage at the pupil margin, so that it may or may not be pathological in patients over that age.

The neovascular changes in the iris in anterior segment pigment dispersal syndrome were not as marked as those in pseudoexfoliation of the lens capsule,¹² which seems to be a more active and rapidly developing pathological process. Nor were they as marked as those occurring in chronic cyclitis or iritis.¹³ They were far less marked than those seen in neovascular glaucoma following central retinal vein occlusion or in diabetic neovascularisation of the iris.¹⁴ This is probably because neovascular change in pigmentary glaucoma develops very gradually owing to a congenital defect, while the other forms of neovascular change develop more rapidly and in neovascular glaucoma very rapidly indeed.

We believe these findings on iris angiography in anterior segment pigment dispersal syndrome indicate hypoperfusion of the iris even in young patients together with a mild degree of neovascularisation.

These changes are present, though less marked, in the relatively unaffected eye when the pigment dispersal is virtually unilateral. This suggests that the mesodermal and vascular changes precede the

clinical appearance of the anterior segment pigment dispersal syndrome.

Marked hypoplasia of the iris stroma was noted in some eyes, and this was sometimes accompanied by an apparent shrinkage of the iris, so that the pupils became wide and semidilated, though still reacting to light and accommodation. Ectropion uveae did not occur, but atrophy of the iris stroma seemed to be progressive in patients watched over a long time.

We postulate that the hypovascularity of the iris is of very long standing, probably being congenital in origin, so that the other changes in the iris also develop slowly. Neovascular changes, probably secondary to the hypovascularity, are not very marked and their development is subtle. Hypoplasia of the stroma may be partly congenital in origin like the hypovascularity and partly secondary to it. The hypoplastic, hypoperfused iris stroma makes a poor support tissue for the iris pigment epithelium, which is therefore susceptible to degenerative change and release of its pigment granules.

We further suggest that the pigment release in anterior segment pigment dispersal syndrome is due to the congenital mesodermal deficiency of the iris stroma. The ultimate cause of the pigment release may be mechanical, as suggested by Campbell,⁴ by rubbing of the iris against the ciliary packets, especially in myopic eyes, but in a recent series⁹ most eyes were not myopic and most of the myopia was less than 2.0 dioptres.

It is likely that the pigment release from the iris epithelium and its deposition elsewhere in the anterior segment, especially in the trabecular meshwork, cause obstruction to aqueous outflow and rise in intraocular pressure. Some eyes may be more susceptible to this effect than others, and this may be the case with the well marked iris processes seen in pigmentary glaucoma.

It has been noted that patients with pigmentary glaucoma are often tense, and attacks of high rise in pressure may be precipitated by physical exertion or emotional stress.¹⁵ The dilator muscle of the iris is under sympathetic control and is inserted into the iris peripherally in the region of greatest pigment release from the iris. Perhaps this is the final mechanism of pigment release, and, as iris mobility decreases with age and treatment, there is diminished shedding of pigment granules, which has been noted to occur in time.¹⁶

Whatever the final mechanism of pigment release, a consideration of the findings on iris angiography and the low grade iris hypoplasia and hypovascularity in the condition suggests that the underlying cause is a congenital deficiency of the mesodermal support tissue of the iris, which occurs early in development and is probably congenital.

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Light microscopic and electron microscopic histopathology of an iris microhaemangioma

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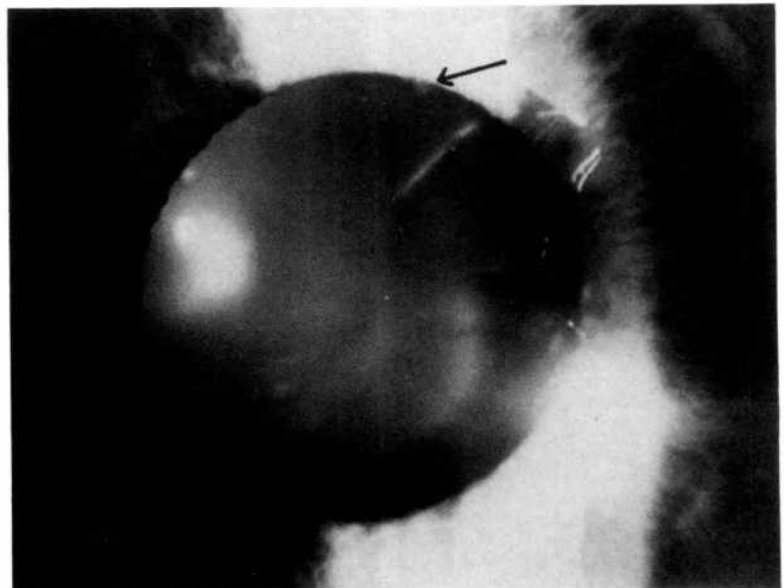
SUMMARY A patient who had been observed to have an iris microhaemangioma (capillary haemangioma), confirmed on fluorescein iris angiography, came to cataract surgery. The lesion was excised at the time of surgery and submitted to light and electron microscopic study. It had the features of a hamartoma of the capillary haemangioma type, with its characteristics being specific for vessels seen in iris tissue.

Iris microhaemangiomas (IMHs) (capillary haemangiomas) are vascular tufts usually found at the pupillary margin, but occasionally they are situated in the anterior stroma. Usually they are found in older people (over 60 years) and are better seen with an undilated pupil. Their association with diabetes mellitus, chronic obstructive airways disease, and myotonic dystrophy has been noted.¹⁻⁴

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IMHs consist of tightly coiled blood vessels with capillary-like walls, and have an overall size of 150 μ . They have also been described as an aggregation of blood vessels at the pupillary border,¹ but there have been few histopathological studies. Amasio *et al*⁵ described them as abnormal blood vessels that destroyed and replaced iris stroma and were composed of fissures paved with endothelial cells. Both Ashton⁶ and Cashell⁷ described them as thin walled vessels, associated with some connective tissue.

Fig. 1 Iris microhaemangioma on slit-lamp examination.



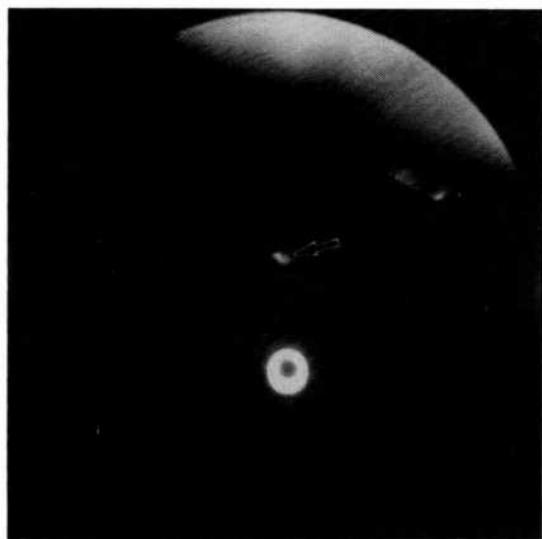


Fig. 2 Iris fluorescein angiogram.

Knapp⁸ thought that the endothelial cells proliferated, forming a nodular protuberance, and Anderson and Øther⁹ thought they were a cystic lesion caused by the dilatation of a vein.

Iris fluorescein angiography (IFA) has been used to investigate these lesions and help to distinguish them from vascular malignant melanomas.⁵ They are seen as multiple hyperfluorescent dots at the pupillary border,^{4,10} and IFA shows them to be more numerous than their appearance on slit-lamp examination suggests.¹¹ IFA has shown leakage from the vessels of the IMH into the aqueous,¹² but fluorescein leakage has also been noted from normal pupillary vessels with increasing age.^{13,14}

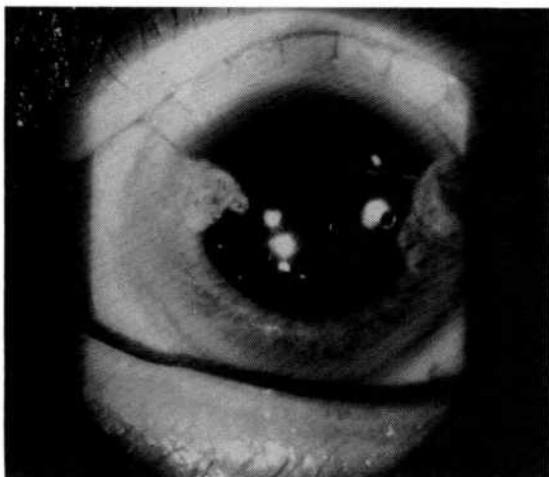


Fig. 3 Cataract extraction with posterior chamber intraocular lens and sector iridectomy.

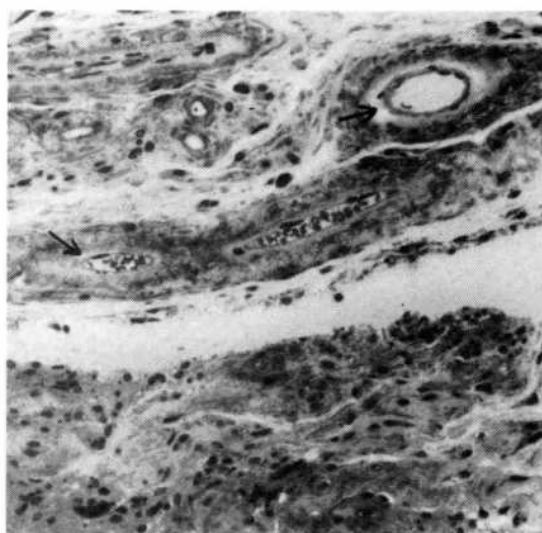


Fig. 4 Light photomicrograph of an IMH. Note the 'thick walls' (arrows) of normal iris stromal blood vessels. (Toluidine blue stain, $\times 256$).

IMHs are important clinically because they have been cited as a cause of spontaneous hyphaema and secondary glaucoma.^{1,15-17}

Case report

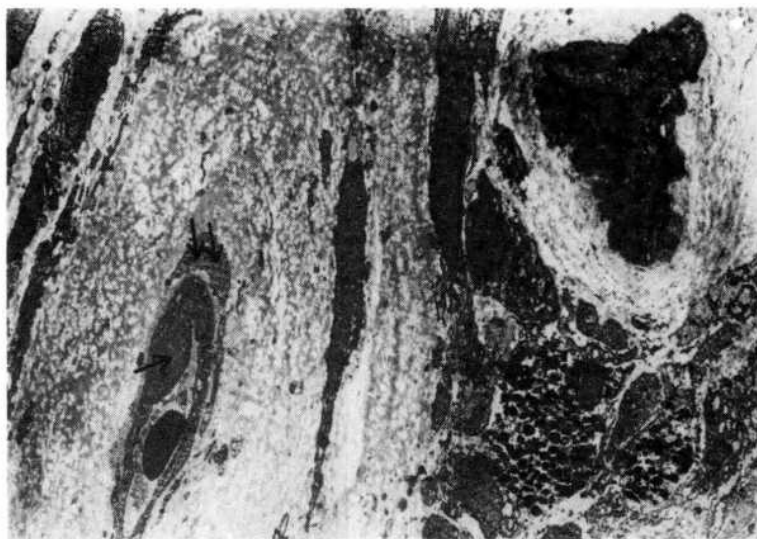
A 79-year-old male who had mild congestive failure and chronic obstructive airways disease and a history of glaucoma and cataracts was observed in 1980 to have a right IMH at 1 o'clock on the pupillary border (Fig. 1). The vascular nature of the lesion was confirmed on IFA (Fig. 2). The patient's vision was reduced to 6/12 part in the right eye, and 6/18 part in the left eye, owing to cataracts. He was on timolol drops for his chronic glaucoma, with intraocular pressures in the low teens. An IMH was visible on his left superior pupillary border also. He was visually asymptomatic at that time and remained so until two years later, when he presented for cataract surgery because of failing vision. His vision in the right eye at that stage was 6/24.

A right extracapsular cataract extraction with posterior chamber intraocular lens implantation and sector iridectomy was performed (Fig. 3). There were no operative or postoperative complications. The iridectomy enabled the IMH to be removed intact, and the specimen was submitted for light microscopic and electron microscopic histopathology.

RESULTS OF HISTOPATHOLOGY

Histologically an IMH appears to be a hamartoma (a mass of tissue normally found at the involved site)

Fig. 5 Electron photomicrograph of the stromal vessels of an IMH lined with endothelial cells (arrow) and pericytes (double arrow) in a basement membrane which connects with the surrounding tissue. ($\times 2000$).



composed primarily of iris stromal blood vessels. The 'thick walls' of these vessels, seen in the light photomicrograph (Fig. 4) are due to the arrangement of endothelial cells and pericytes surrounded by loose connective tissue.

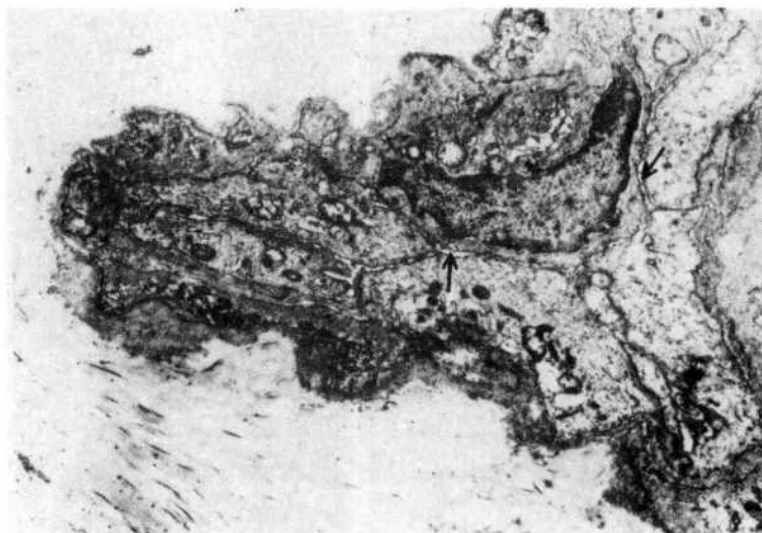
On electron microscopy these stromal vessels are lined with typical endothelial cells of normal thickness (Fig. 5) with no fenestrations, and joined at their apices by terminal bars composed of zonula occludens and zonula adherens. These terminal bars are better seen in Figs. 6 and 7. The apical portion (zonula occludens) consists of dense plasma membranes so closely apposed that there appears to be no intercellular space. The zonula adherens (on the

basal aspect of the zonula occludens) resembles a desmosome, but its intercellular space is narrower than that of a desmosome. Endothelial cells and pericytes lining the capillary are enveloped in a basement membrane, which connects with the surrounding loose connective tissue (Fig. 8).

Discussion

Normal iris capillaries have a bilaminar structure, with a loose connective tissue enclosing basement membrane, endothelial cells, and pericytes. This connective tissue connects the capillary with the surrounding iris stroma. Such a structure allows the

Fig. 6 The lumen of the vessel in the upper right of Fig. 5 is compressed to a branching slit (arrows). The apical junctions of the endothelial cell are intact. ($\times 5000$).



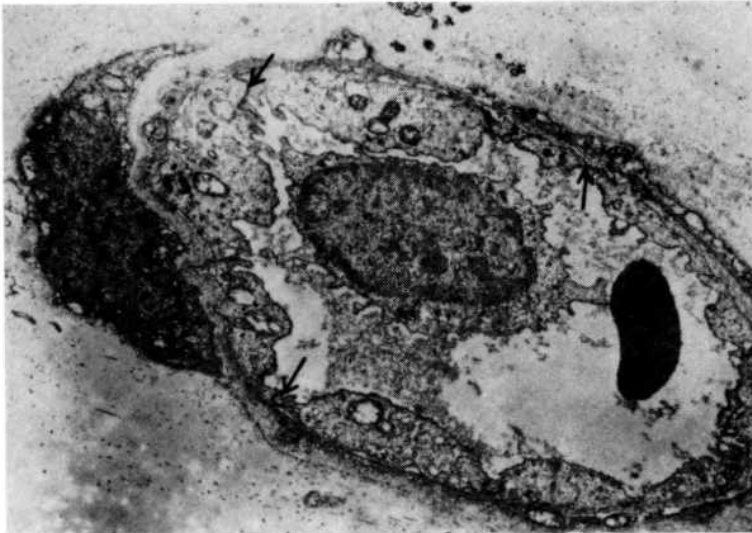


Fig. 7 The lumen of this stromal vessel in the IMH is open. Endothelial cells are joined at their apices by terminal bars (arrows). ($\times 5000$).

capillary to remain patent on movements of the iris and gives the stromal iris blood vessels a typical 'thick walled' appearance. The endothelial cells are non-fenestrated and are joined by terminal bars.

The histology of the IMH described therefore shows them to be hamartomas consisting of iris stromal blood vessels. This case report accurately describes the light microscopic findings and electron microscopic findings of this lesion.

Daidoff *et al.*¹⁸ described abnormal iris vessels in a peripheral lesion of the iris in a case of diffuse congenital haemangiomatosis, but this lesion was a cavernous haemangioma, not a microhaemangioma, and electron microscopy was not done on the iris

lesion. Knapp⁸ also described a case of generalised vascular naevi with abnormal blood vessels, but again this was a much larger lesion than an IMH.

Some authors^{5,6,9,19,20} have described the angiomatous blood vessels as being dilated with thinned endothelial cells invaded by connective tissue, but electron microscopic studies have not been performed.

In contrast, one electron microscopic study of iris neovascularisation by Ringvold and Davanger²¹ showed a narrowing of the blood vessel lumen with an increase in volume of the endothelial cells and tight junctions between the cells. The basement membrane was thin and broken, and the endothelial

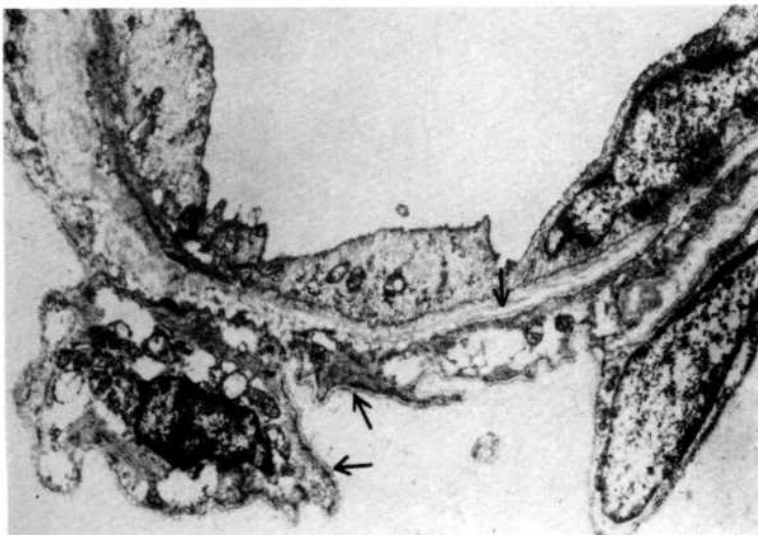


Fig. 8 Another stromal vessel lined with endothelial cells (with intact apical junctions) and pericytes enveloped in a basement membrane (arrows) connecting with the surrounding tissue. ($\times 5000$).

cells were fenestrated. On IFA the fluorescein was localised to the neovascularised area, and the appearance was attributed to gaps in the interendothelial junctions or to endothelial fenestration.

In cases of IMHs, IFA has sometimes shown leakage from angiomatic vessels,^{11,12} but this has also been seen in normal stromal blood vessels with increasing age.^{13,14} The leak can be explained by breaks in the endothelial cells rather than gaps between the cells.

In conclusion, we believe this to be the first electron microscopic description of an iris microhaemangioma, indicating it to be a true hamartoma of the iris stromal blood vessels.

We thank Miss Robyn Morgan for typing the manuscript in the preparation of this paper

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TECHNICAL DATA OVERLEAF



TECHNICAL DATA

DATA SHEET

PDS* (Polydioxanone) Sterilised Absorbable Synthetic Monofilament Suture

Presentation

PDS (Polydioxanone) Monofilament Synthetic Absorbable Suture is prepared from the polyester poly (p-dioxanone). The empirical molecular formula of the polymer is $(C_{12}H_{16}O_5)_n$. PDS (Polydioxanone) sutures are coloured by adding D & C blue No 6 (gauge 0.2 metric and 0.3 metric) D&C violet No 2 (gauge 0.4 metric to 5 metric) during polymerisation. These sutures may also be manufactured undyed (clear).

PDS (Polydioxanone) sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action

Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second absorption rate or loss of mass.

Data obtained from implantation studies in rats show that, at two weeks post implantation, approximately 70% of the suture strength is retained whilst at four weeks the strength retention is approximately 50%. At eight weeks approximately 14% of the original strength remains. This indicates a significantly longer period of wound support than previously available with an absorbable suture.

The absorption or loss of mass is minimal until about the 90th post implantation day and is essentially complete within six months.

Uses

PDS (Polydioxanone) monofilament sutures are intended for use where an absorbable suture or ligature is indicated. They may have particular application where longer wound support is required. See strength retention data above.

Dosage and Administration By implantation

Contra-indications, Warnings, etc.

These sutures, being absorbable, should not be used where extended approximation of tissue under stress is required.

As with all monofilament synthetic sutures, care should be taken to ensure proper knot security.

Conjunctival, cuticular and vaginal mucosal sutures could cause localised irritation if left in place for longer than 10 days and should be removed as indicated. Superficial placement of subcuticular sutures may also be associated with erythema and reaction during the course of absorption.

The safety and effectiveness of PDS (Polydioxanone) sutures in neural and cardiovascular tissue have not yet been established. The use of the material in the renal tract is currently under investigation.

Pharmaceutical Precautions Do not re-sterilise

Legal Category P

Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Packaging

The gauge range available will be 0.3 metric (9/0) to 5 metric (2). Various lengths of material attached to non-traumatic stainless steel needles are packaged in sealed aluminium foil sachets.

The primary pack is sealed within a peel-apart secondary pouch and contained in a film-wrapped drawer style carton.

Further Information

No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence Nos PL 0508/0011 (dyed), PL 0508/0012 (clear)

Br Pat No 1 540 003

Date of preparation of Data Sheet—September 1982
Revised 1/1988

DATA SHEET

Coated VICRYL* (Polyglactin 910) Sterilised Absorbable Synthetic Braided Suture

Presentation

The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_3H_4O_3)_m(C_3H_4O_2)_n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

Coated VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Suture may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action

Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses

Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration By implantation

Contra-indications, Warnings, etc.

These sutures, being absorbable, should not be used where extended approximation of tissue under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 10 days and should be removed as indicated.

The safety and effectiveness of Coated VICRYL (Polyglactin 910) Sutures in neural tissue and in cardio-vascular tissue have not been established.

Pharmaceutical Precautions Do not re-sterilise

Legal Category P

Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities

Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sale is 12 packs contained in a film wrapped drawer style carton.

Further Information

No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence No PL 0508/0009
Br Pat No 1063360

Date of preparation of Data Sheet—April 1981
Revised 1/1985

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Iridotomy with red krypton laser

Y YASSUR, R DAVID, I ROSENBLATT, AND U MARMOUR

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SUMMARY Iridotomy with red krypton laser instead of blue-green argon laser was performed on 68 eyes with various types of angle-closure glaucoma. Patent iridotomy was obtained in all the eyes, mostly in one working session. In eight eyes secondary closure by pigment needed reopening with a few applications at the iridotomy site. There were no immediate or late complications of importance, the main advantage of the technique being the avoidance of the corneal epithelial and endothelial burns which commonly occur during argon laser iridotomy, particularly when the anterior chamber is shallow.

Laser iridotomy has successfully replaced surgical iridectomy as a therapeutic procedure in patients with angle-closure glaucoma.^{1,2} The results reported were satisfactory both when the cool-mode, pulsed lasers and the continuous wave argon laser² were used. The most popular technique employed is treating the iris periphery with 50 μ m spots, at intensities of 800-1200 milliwatts and exposure time of 0.1-0.5 second, until a through-and-through hole in the iris is obtained.^{3,4}

A different technique with the continuous wave, blue-green argon laser has been advocated by Yassur and his coworkers.⁵ This involved the delivery of high laser power (3-4 watts) in short exposures of 0.01-0.04 second. The main advantage of this method is the reduction of heat dissipation during the procedure.

More recently the introduction of YAG lasers (Q-switched and mode-locked) provided ophthalmologists with a new tool which has a real cutting effect. Iridotomy was shown to be obtained with a relatively low energy (3-5 millijoules) after one or two applications.^{6,7}

We present here our experience in the last two years with the alternative technique for iridotomy as previously described⁵ but using the red krypton laser instead of the argon laser.

Material and methods

OPERATIVE TECHNIQUE

The instrument used was the argon-krypton laser

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photocoagulator made by Lasertek, Finland. The red krypton laser was set for maximum power (800-1000 milliwatts at the cornea). Spot size was 50 μ m and exposure time 0.01-0.04 second. The iridotomy site was around the 12 o'clock meridian, 1-3 mm from the limbus. Pre- and postoperative care was as described for argon laser iridotomy⁵; it included pilocarpine 2% prior to the laser applications and three to four instillations of an antibiotic-steroid compound eye drop during the 24 hours after the iridotomy. The laser applications were delivered through an Abraham's contact lens, and the intra-ocular pressure was monitored for two to four hours postoperatively. If during this period an increase in pressure of more than 5 mmHg was detected, acetazolamide was administered orally and the pressure monitored for the next 24 hours.

PATIENTS

A total of 68 eyes were treated by this technique and the patients followed for at least six months. The diseases for which the iridotomy was indicated were the following: acute angle-closure glaucoma, 21 eyes; fellow eyes of patients after acute angle-closure, 37 eyes; chronic angle-closure glaucoma, 10 eyes; total, 68 eyes.

Of these 68 eyes 61 were in patients with dark irides and seven in patients with pale irides. All the patients were followed up for 6-24 months.

Results

In all 68 eyes a patent iridotomy was obtained. The number of applications necessary to obtain a 200-400

μm iridotomy ranged from a minimum of 22 to a maximum of 168, mean 52. When a wider iridotomy was required, more applications were carried out. The exposure time was 0.01 s in 16 eyes, 0.02 s in 22 eyes, and 0.03 s in 24 eyes. Only six eyes needed 0.04 s exposure, and none of the eyes needed a longer exposure time than 0.04 s.

In 59 eyes the iridotomy was accomplished in one session and in nine eyes a second session was necessary. Secondary closure of the iridotomy by pigment occurred in eight eyes (seven dark and one blue) and it was reopened by 1–10 applications. Occasionally a slightly dragged-up pupil at the end of the procedure was noticed, and the pupils regained their round shape spontaneously, within a few days to two weeks after the operation.

The most important feature of the technique was that no visible damage to the cornea was observed, except in two eyes in which a mild, transitory, local stippling of the endothelium was noticed. In all the other eyes the endothelium remained clear even when the iridocorneal space was very narrow at the iridotomy site.

A transient increase in pressure and/or iritis were noted as frequently as with argon laser iridotomy by the high-power short-exposure technique.¹

Focal lenticular opacity was noticed in 21 eyes. These never expanded, and soon either disappeared or became less intense during the follow-up period.

No choroidal or retinal damage could be detected in any of the treated eyes.

Discussion

Robin and Pollack recently reported⁴ that YAG laser iridotomies were superior to argon laser iridotomies for several reasons: less energy used, fewer pulses, less endothelial damage, less focal cataracts, and less secondary cataract. On the other hand severe complications after YAG laser iridotomy irradiation have also been reported. Khodadoust and his co-workers⁸ reported on severe corneal damage from the YAG laser even when the focus of the laser was 3.5 mm away on either side of the cornea.

Awaiting more experience with the YAG laser, many ophthalmologists have not purchased it yet, while many of those who have are still hesitant about using it for iridotomies, particularly in phakic eyes. Thus at present argon laser iridotomy remains the procedure preferred by most. Quite often, however, corneal epithelial and endothelial burns occur during argon laser iridotomy, and the transient opacities which accompany these burns may interfere with visibility and jeopardise the achievement of the iridotomy in that session. This is apt to occur in patients with pre-existing peripheral corneal

opacities, which dictate the use of higher argon laser power, and in eyes which have a very shallow peripheral anterior chamber, which is not uncommon in patients with angle closure.

The theoretical considerations which guided us to use red krypton laser for this procedure rather than argon laser were based on the physical properties of spectral red light as shown in absorption, scatter, and transmission curves. It is readily transmitted through human cornea, and it is less scattered or absorbed by corneal opacities^{9,10} than the argon laser. It is also well absorbed by the uveal pigment.^{11,12}

These properties, which enable red light to reach the iris pigment more efficiently, enable us to achieve patent iridotomy quite easily by using less energy than with the argon laser. When a patent iridotomy is not obtained in a single session with the red krypton laser, the failure is not due to focal corneal opacity at the iridotomy site but to other causes, such as the patient's failure in compliance or the surgeon's attempt to avoid the tendency to transient pressure elevation, as in chronic angle-closure glaucoma.

We therefore recommend that, whenever continuous-wave laser iridotomy is preferred to the neodymium-YAG laser, the red krypton laser should be used instead of the argon laser. This technique may enable the surgeon to achieve a patent iridotomy by using less energy and causing less corneal damage, which, although it is transitory, may be troublesome when iridotomy at one session is aimed for, and in eyes with a very shallow anterior chamber.

This study has been partly supported by a grant from the Middle East Eye Research Institute, Ben-Gurion University, Beer-Sheva, Israel.

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Intraocular injection of Depomedrone

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SUMMARY A case of inadvertent intraocular injection of Depomedrone (methylprednisolone acetate) and its management by vitrectomy is discussed, with a review of previously reported cases.

The administration of steroids by retrobulbar or orbital floor injection has been established as an effective¹ and safe² procedure. Accidental perforation of the globe and intraocular injection of a large bolus of steroids is an unusual but well documented complication and is known to carry a poor prognosis for vision.³ Here we report on the outcome and the effects on the retinal function of a patient who suffered an accidental intraocular injection of Depomedrone (methylprednisolone acetate).

Case report

CLINICAL COURSE

A 65-year-old female patient was referred to Moorfields Eye Hospital after an inadvertent injection of 0.7 ml of Depomedrone into the right vitreous cavity eight hours previously. She had been receiving regular retrobulbar injections of Depomedrone (methylprednisolone acetate) as a treatment for macular oedema. That day the injection was performed via the upper nasal fornix and was apparently uneventful. The patient did not experience any undue discomfort but did notice immediate blurring of vision. She returned to the referring ophthalmologist six hours later as the vision in the right eye had failed to improve during the course of the day.

The patient was known to have been a high myope and 10 years previously had undergone bilateral intracapsular cataract extractions. The last recorded visual acuity was 6/18 in the right eye and 6/60 in the left eye.

On admission to hospital the patient's right visual acuity was perception of light only. Vision in the left eye was reduced to the level of counting fingers due to severe myopic degeneration. The conjunctiva of the right eye was injected, but the cornea was clear.

There was a marked right afferent pupillary defect. The intraocular pressures were 0 mmHg in the right eye and 14 mmHg in the left. Large white deposits were present on the iris and in the anterior chamber angle. The vitreous was cloudy, with large white clumps throughout the anterior gel obscuring the view of the right retina.

The left eye was aphakic, and there was extensive myopic degeneration of the posterior pole.

Ultrasound examination of the right eye suggested a detached vitreous gel, and the retina was apparently attached. In view of the potential posterior

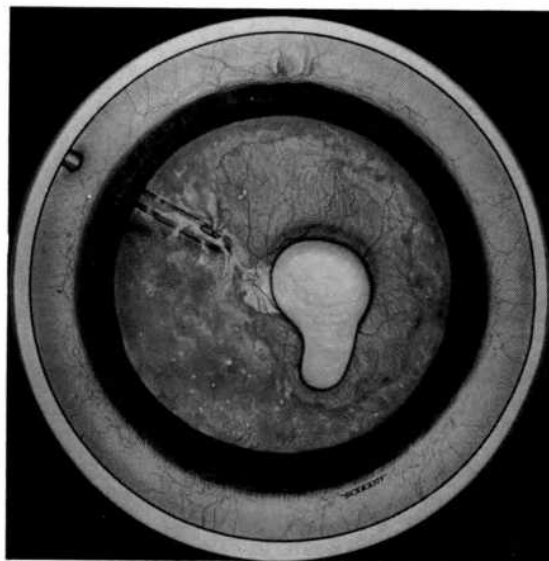


Fig. 1 The artist's impression of the operative findings at vitrectomy following the removal of the central portion of the opaque posterior hyaloid face. A discreet mass of the drug is layered over the posterior pole. Note the small deposit of the drug under the superonasal retinal vein, presumed site of ocular penetration. (The fibro-optic light probe and the infusion terminal have been omitted from the painting.)

segment complications, pars plana vitrectomy was performed on the same night.

At operation Depomedrone was removed by suction from the anterior chamber and by vitrectomy from the posterior segment. The drug was found to be layered over the posterior pole and a small collection of subretinal Depomedrone was found in the superonasal quadrant (Fig. 1). The vitreous cavity was reconstituted with Hartmann solution and a subconjunctival injection of cephaloridine was given.

On the first postoperative day the eye was comfortable, but the visual acuity was hand movements only. There was stromal and epithelial oedema of the cornea, but this cleared during the following three days. The right relative afferent pupillary defect which was present at first diminished gradually, becoming equivocal by the third postoperative day.

The retina remained attached throughout the postoperative period, and at no time was there any clinical evidence of epiretinal membrane proliferation. Fluorescein angiography performed at the end of the first postoperative week and again one month later did not show leakage from retinal capillaries or macular oedema.

Over the next four weeks the visual acuity improved to 6/36, and it remained so during the subsequent 12 months

ELECTRORETINOGRAPHY

In addition to the clinical follow-up serial electroretinography was performed during the immediate postoperative period and thereafter at two-monthly intervals. We used Arden's modified method as described elsewhere.⁴

The amplitudes of the b wave were reduced in each eye. This reduction was thought to be consistent with the bilateral myopic degeneration. With the bright stimulus the recording from the operated eye showed a rise in the voltage of the b wave from 80 μ V to 180 μ V in the first 10 days, and over the next five months

the voltage ranged from 175 μ V to 280 μ V. There was no significant change in the peak implicit time. The b wave amplitude of the fellow eye was 180 μ V immediately after the operation, and thereafter it remained in the range 200 μ V to 240 μ V.

The b wave amplitudes of the two eyes were compared, and the resulting ratio showed the recovery of the affected eye (Fig. 2).

Discussion

Periocular injection of methylprednisolone acetate has been used as a treatment of intraocular inflammation for over 20 years.⁵ The recognised complications of such injections include glaucoma, posterior subcapsular lens opacities, scarring of Tenon's capsule, paralysis of extraocular muscles, atrophy of subcutaneous tissues of the inferior orbital rim, and inadvertent intraocular administration.^{6,7}

To our knowledge only 12 other cases of inadvertent intraocular injection of methylprednisolone have been recorded so far.⁸⁻¹¹ Most were managed conservatively and the majority suffered serious complications: five developed complex retinal detachment, one an extensive preretinal membrane, and another ascending optic atrophy. A recent report suggests vitrectomy as a useful alternative to conservative management,⁹ and the visual result in our case showed that early surgery can offer a better prognosis in this type of injury.

It was interesting to correlate the return of the visual function with the results of the serial electrophysiological tests. While we are aware that intraocular procedures such as vitrectomy may decrease electroretinographic responses, the profound depression of the wave form in our case was in excess of that usually observed after 'simple' vitrectomy without intraocular tamponade.¹² Rather, direct retinal toxicity of one or more components of the drug was more likely to have produced such marked electrophysiological changes.

Each ml of Depomedrone contains: methylprednisolone acetate 40 mg; polyethylene glycol 4000 29 mg; sodium chloride 8.7 mg; myristyl-gamma-picolinium chloride 0.19 mg; water for injection; and the pH is 5.6-6.5.

The dosage and toxicity of steroids for intraocular use in the treatment of intraocular infections and proliferative retinopathy is well documented.^{13,14} However, the suggested safe dose of triamcinolone for intraocular use is 20 times less than the equivalent dose of methylprednisolone injected into the eye of our patient.^{15,16}

Of the other constituents polyethylene glycol is a detergent and is known to be capable of producing arachnoiditis and pachymeningitis in humans.^{17,18}

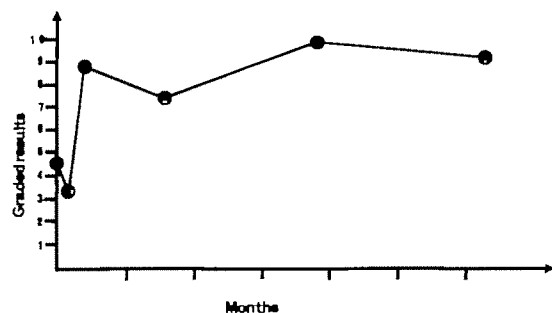


Fig. 2 The ratio of the amplitude of the b wave of the injured eye was compared with that of the fellow eye. The ratios are presented as graded results over a period of eight months

Myristyl-gamma-picolinium chloride is a germicidal as well as a detergent substance and is considered safe in concentrations up to 1 in 1000¹⁰. In Depomedrone its concentration is only 1 in 5000. The low pH of Depomedrone may have also contributed to the depression of retinal function.

Thus we consider that in cases such as ours the immediate removal of the drug by vitrectomy achieved not only an early visual rehabilitation but also minimised its long-term toxic effects on retinal function.

We thank Mr Richard Carter for his help with the electroretinograms and Miss Deborah Hollingsworth for the secretarial assistance

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Oral doxycycline in the treatment of adult chlamydial ophthalmia

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SUMMARY Ninety-three consecutive patients with adult chlamydial ophthalmia were treated with four different regimens of oral doxycycline. In patients treated with a single dose of 5 mg/kg of body weight (300 mg) of doxycycline the severity of clinical signs was reduced, and in half of the patients shedding of the infective agent was stopped. Treatment with a weekly dose of 300 mg of doxycycline for three weeks or a daily dose of 1.5 mg/kg of body weight (100 mg) for one week produced a clinical and microbiological cure in 100% of patients. However, in some of these patients mild to moderate papillary responses were present up to six months from completion of the treatment. The best results were obtained with a daily dose of 100 mg for two weeks, which produced rapid clinical and microbiological cure in all patients.

Adult chlamydial ophthalmia (ACO) or paratrachoma includes inclusion conjunctivitis, TRIC-agent punctate keratoconjunctivitis, and trachoma of sexually transmitted origin.¹ ACO is generally associated with a concurrent, but mainly asymptomatic, chlamydial genital infection in the patient and/or in the patient's consort(s).^{2,3} It is estimated that in the developed countries approximately 1% of the patients with a chlamydial genital infection may develop ACO (unpublished data). However, the prevalence of ACO is increasing because of the rising prevalence of chlamydial genital infections.⁴

ACO has been shown to respond well to topical treatment with tetracycline or rifampicin eye ointment when used for a minimum period of six weeks.^{5,6} However, the major setback in this method of therapy is the patient's poor compliance owing to difficulty with correct application of ointment and the long course of treatment. In addition the concurrent genital infection remains untreated, which may cause reinfection of the eye or other severe complications such as endometritis, pelvic inflammatory disease in women, and infertility in men and women.^{7,8} Oral therapy with systemic tetracycline has been shown to be effective against chlamydial genital infections⁹ and trachoma.¹⁰

In this report we present the results of an open trial

of the efficacy of various regimens of therapy with oral doxycycline, a long-acting synthetic derivative of tetracycline, in the treatment of ACO.

Patients and methods

Patients. Patients attending the External Eye Diseases Clinic, Moorfields Eye Hospital, with a moderate or severe follicular conjunctivitis with or without keratitis and with a positive culture test for *Chlamydia trachomatis* were included. The patients were examined with a Haag-Streit 900 slit-lamp and the symptoms and signs observed in the whole of the conjunctiva (i.e., upper tarsus, upper fornix, and lower lid) and cornea were graded on a 0-3 scale following the method described earlier.⁵ Clinical scores were calculated by adding the individual scores for symptoms and signs from all areas of the conjunctiva and cornea. Patients were considered to be clinically cured when they had a clinical score of less than 10.

Chlamydial Isolation. Swabbings were collected from the whole conjunctiva and placed in plastic vials containing 2SP transport medium¹¹ with 3% fetal bovine serum. The methods of storage and transport of the conjunctival specimens and culture in irradiated McCoy cells are described elsewhere.¹²⁻¹⁴

Medication. Consecutive patients were treated with doxycycline on one of the following regimens: (a) a single dose of 300 mg (5 mg/kg body weight);

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(b) a weekly dose of 300 mg for three weeks; (c) an initial dose of 300 mg on the first day followed by a daily dose of 100 mg (1.5 mg/kg body weight) for one week; (d) an initial dose of 300 mg on the first day followed by a daily dose of 100 mg for two weeks. The patients were advised to take the drug after a meal.

Follow-up. Treatment was begun after the initial clinical and laboratory investigations. Follow-up clinical examinations and culture tests were carried out at weekly intervals for four weeks, then at six weeks, eight weeks, 12 weeks, six months and 12 months.

Results

Ninety-three consecutive patients with moderate to severe ACO and a positive culture for *C. trachomatis* were included in this study. The ages of the patients ranged from 16 years to 45 years, the majority being between 18 and 30 years old. There were 47 male and 46 female patients.

Single dose treatment. Eleven patients were treated with a single dose of doxycycline and followed up for eight weeks. Clinically no patient was cured (Table

1), but the intensity of inflammatory responses in all of these patients was substantially reduced (Table 2, Fig. 1). Microbiologically, four of the nine (44%) patients who attended regularly were culture negative at eight weeks (Table 2). However, because of the continuing presence of active clinical signs and/or positive culture tests, these patients were subsequently treated with 1% rifampicin eye ointment and were referred to our Genito-Urinary Medicine Clinic for investigation and management of probable chlamydial genital tract infection.

Weekly dose for three weeks. At 12 weeks 17 of the 22 patients treated on this regimen had completed their follow-up examinations. In all these patients clinical and microbiological cures were obtained (Table 1, Figs. 1 and 2). However, 5 of the 17 patients had persistent mild to moderate papillary responses up to six months after completion of treatment. These papillary responses resolved with no further treatment.

Daily dose for one week. All the 12 patients who were followed up at 12 weeks were microbiologically and clinically cured (Table 2; Figs. 1 and 2). Clinically three of the 12 patients showed papillary

Table 1 Number of patients cured following treatment with oral doxycycline

Treatment regimen	No of patients	Four weeks clinical	culture*	Eight weeks clinical	culture†	12 Weeks clinical	culture‡
Single dose (300 mg)	11	0/11	5/11 (45%)	0/11	4/9 (44%)	Not done	Not done
Three weekly doses (300 mg)	22	14/22 (64%)	22/22 (100%)	14/22 (64%)	20/22 (91%)	17/17 (100%)	17/17 (100%)
One week (100 mg daily)	15	12/15 (80%)	15/15 (100%)	13/15 (87%)	13/13 (100%)	12/12 (100%)	12/12 (100%)
Two weeks (100 mg daily)	45	43/45 (96%)	45/45 (100%)	45/45 (100%)	43/43 (100%)	39/39 (100%)	39/39 (100%)

*Four weeks after beginning of treatment

†Eight weeks after beginning of treatment

‡Twelve weeks after beginning of treatment.

Table 2 Effect of different treatment regimens on clinical scores and isolation of *C. trachomatis*

Treatment Regimen	Number of patients	Time after commencement of treatment											
		Before		1 Week after		2 Weeks after		4 Weeks after		8 Weeks after		12 Weeks after	
		Aver. clin. score	No. of positives	Aver. clin. score	No. of positives	Aver. clin. score	No. of positives	Aver. clin. score	No. of positives	Aver. clin. score	No. of positives	Aver. clin. score	No. of positives
Single dose (300 mg)	11	42	11/11 (100%)	26	3/11 (27%)	22	8/11 (73%)	26	5/11 (45%)	22	4/9 (44%)		
Three weekly doses (300 mg)	22	42	22/22 (100%)	26	2/22 (9%)	18	2/22 (9%)	16	0/22 (0%)	12	2/22 (9%)	9	0/17
One week (100 mg daily)	15	39	15/15 (100%)	21	1/15 (7%)	18	0/15 (0%)	13	0/15 (0%)	10	0/13 (0%)	4	0/12
Two weeks (100 mg daily)	45	46	45/45 (100%)	20	2/45 (4%)	16	0/43 (0%)	10	0/45 (0%)	4	0/43 (0%)	2	0/39

Clinical scores <10 trivial, 11–20 mild, 21–30 moderate, 31–40 severe ;

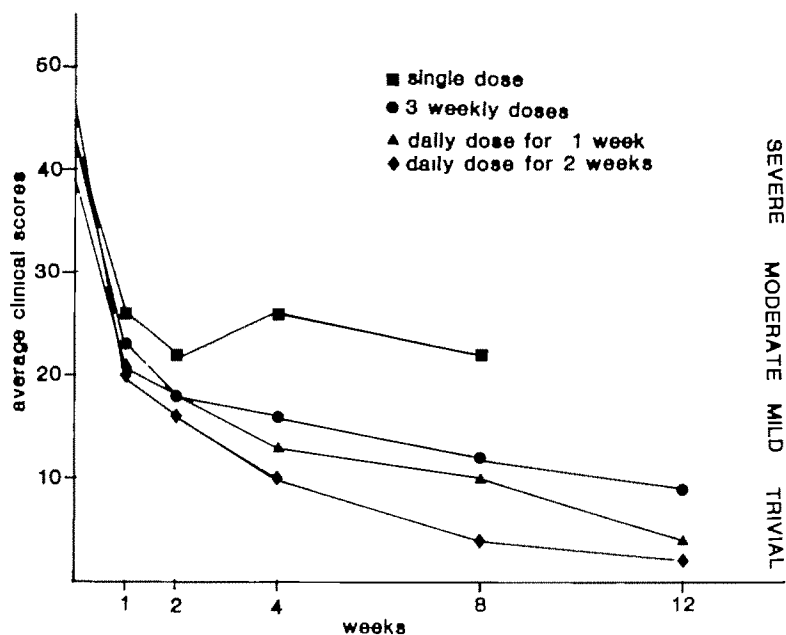


Fig. 1 Clinical response to treatment on various regimens of oral doxycycline.

responses for up to six months after completion of treatment. These papillary responses resolved with no further treatment.

Daily dose for two weeks. All of the 39 patients who were followed up at 12 weeks were clinically and microbiologically cured.

Further follow-up. Further follow-up showed clinical and microbiological cure in those patients who did not attend regularly during the first three months of the study and were not included in the Tables 1 and 2.

Adverse reactions. Two of the 22 patients on

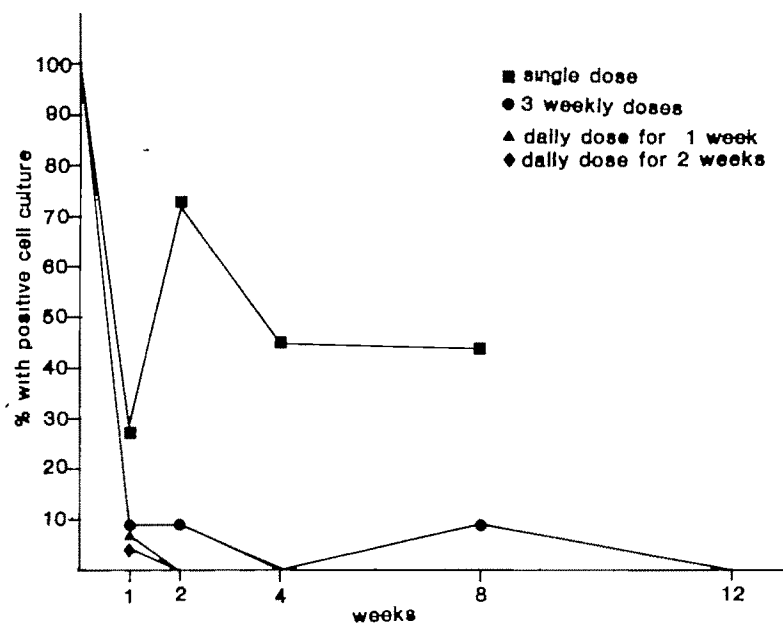


Fig. 2 Microbiological response to treatment on various regimens of oral doxycycline.

weekly doses for three weeks and three patients who received daily treatment for two weeks complained of nausea or epigastric burning.

Discussion

This open treatment trial was designed to find the optimal regimen of treatment with doxycycline for patients with ACO. The results showed that a single dose of 300 mg doxycycline reduces the severity of clinical signs and stops the shedding of *C. trachomatis* in about half of the patients. Treatments with a weekly dose for three weeks or a daily dose for one week were equally effective in producing clinical and microbiological cure in all the patients. However, some of these patients showed persistent papillary responses up to six months after completion of treatment, which resolved with no further treatment. The best result, however, was obtained with a daily dose of 100 mg for two weeks, when a rapid resolution of clinical signs was achieved. This finding is consistent with our previous study of treatment of trachoma with doxycycline in a village in Iran.¹¹

The advantages of therapy with doxycycline over other tetracyclines are that it requires minimal daily dose schedules, which greatly enhance patient compliance; it is better absorbed from the gut; and absorption is not affected by diet.

In this study we did not investigate the patients for the presence of chlamydial genital infections before the start of treatment. Three months after starting it 56 patients who had been treated with weekly or daily doses of doxycycline attended our Genito-Urinary Medicine Clinic. *C. trachomatis* was not isolated from specimens taken from the genital tract of any of these patients. In previous studies it had been shown that in untreated women and men with ACO 90% and 48% respectively had concomitant microbiologically proved genital chlamydial infections. The failure to isolate *C. trachomatis* from the genital tract of treated patients in this study suggests that oral doxycycline therapy can simultaneously cure both ocular and genital chlamydial infections.

The results of this study indicate that one weekly dose of doxycycline for three weeks, or a daily dose for one week, or a daily dose for two weeks are effective in the treatment of ACO and its associated genital infections. However, treatment with a daily

dose of doxycycline for two weeks produced a faster clinical recovery than the other two regimens.

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*Trade Mark

Probably Norrie's disease due to mutation

Two sporadic sibships of two males each, a necropsy of one case, and, given Norrie's disease, a calculation of the gene mutation frequency

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SUMMARY Two sibships, each with two affected males but no other affected family members, are described. All four patients at birth had small eyes with white masses visible behind clear lenses. Support for a diagnosis of Norrie's disease lies in the probable mental retardation and sudden death of one child and mental retardation in the other in one of the families, and strong support in the sensorineural deafness in one child in the other family. A necropsy was performed on the dead child. Both eyes showed the retinae to be totally non-attached. The optic nerves were thin. If the diagnosis is Norrie's disease (highly probable), the birth of the second affected child in each family supports the postulate of a mutation in the X chromosome of a germ cell of a maternal grandparent or an earlier maternal ancestor, no previous member of the family having been affected. That implies a 50% risk of the disease in future male siblings and a 50% risk of the carrier state in female sibs. When only one child is affected, the explanation could also be a mutation in that individual. Given Norrie's disease, we have calculated a mutation rate of 3.9 per million chromosomes in the Scottish population—remarkably similar to the mutation rates calculated for many dominant diseases. A diagnosis of autosomal recessive non-attachment of retina implies a 25% risk to later siblings.

Norrie's disease (congenital oculo-acoustic-cerebral dysplasia)¹⁻⁴ is an unusual cause of blindness at birth or within the first few weeks of life, first described as an entity by Norrie in 1927.² In 1925 Heine¹ recorded a similar condition which he called fetal iritis. White masses of primary vitreous with some blood vessels, which are within completely detached retinae, can be seen behind clear lenses. About 55% of affected patients become mentally retarded or have infantile psychosis¹⁵ and 30% are deaf.⁶ The disease is now well established to be due to an X-linked recessive gene, occurring without any manifestation in the carrier females. These characteristics make the diagnosis reasonably obvious. The differential diagnosis is considered in the discussion.

The present series of two separate sporadic sib-

ships of two males each, with a necropsy in one ('sudden infant death syndrome'), is reported to draw attention to the probable diagnosis of Norrie's disease in spite of the absence of any other affected male family members (a mutation being suspected in a germ cell of a maternal grandparent or other maternal ancestor) and to give an account of necropsy in one case. The main differential diagnosis is autosomal recessive non-attachment of retina. Given Norrie's disease, a mutation rate has been calculated.

Case reports

In family A the history was compiled by personal interview with the parents and the maternal grandmother, while in family B it was obtained from the parents. All were able to give a clear and unequivocal account of the relatives shown in the pedigrees.

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FAMILY A

Case A1

The first born was a normal female with occipitofrontal head circumference of 35.5 cm and birth weight 2.91 kg (Fig. 1).

The second child was a male who was noted to have white pupils at birth. The birth weight was 3.29 kg and occipitofrontal circumference 33 cm. Examination under anaesthesia was reported to have revealed white fibrous-like masses behind clear lenses in both eyes, but in the right eye a red reflex was visible in one area—significantly without detectable retinal vessels. Apparently at that time no warning was given to the parents of a risk of recurrence. Since the age of about 3 years he has been reported to be severely mentally and physically retarded. No hearing tests have been done. Inversion of chromosome 8 was found as a result of an independent survey of this family. (Several others in the family have the same abnormality but are entirely healthy.)

Case A2

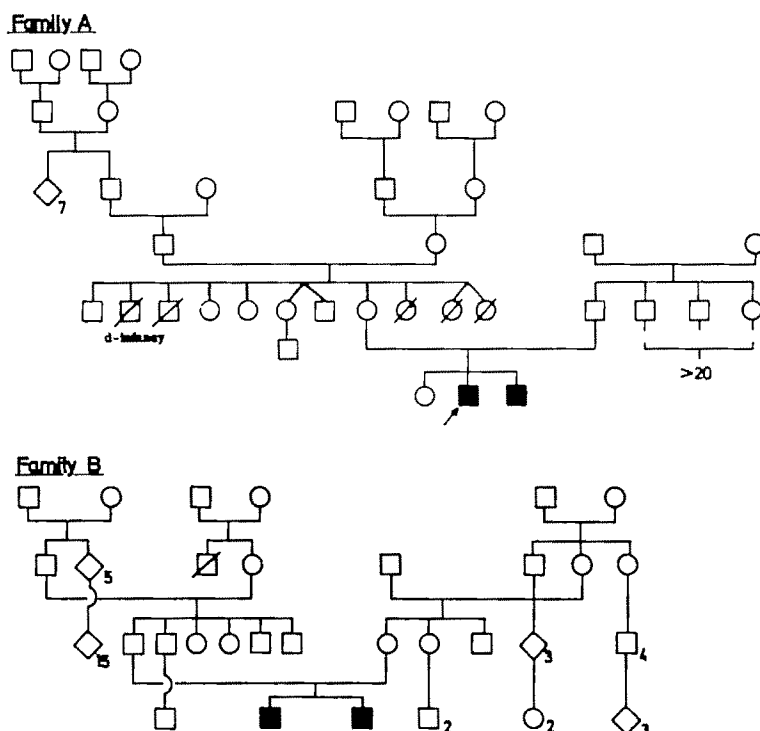
The third pregnancy produced another male, also tragically blind, with a birth weight of 2.63 kg and occipitofrontal circumference 33.4 cm. Under anaesthesia both eyes were seen to be small, with

white retrolental masses. At about six months of age he was investigated because of fits (total of five), each lasting about 30 seconds. He was thought to be developmentally retarded and had an abnormal EEG. He died at the age of 9 months because of 'sudden infant death syndrome', with no suspicion of injury, non-accidental or otherwise. The eyes and brain were obtained for pathological examination, which is reported below. A normal karyotype was found.

The parents were informed that there was a 50% risk of congenital blindness in any future male child and that the daughter, the eldest in the family, had (like any future daughter) a 50% chance of being a carrier, in which case any male child she would have in the future would have a 50% chance of having this disease. The possibility was also mentioned of an autosomal recessive congenital non-attachment of retina, with a 25% risk of recurrence in future siblings of either sex. The parents decided against taking these high risks and the mother has been sterilised.

This family had been the subject of an independent study because of an inversion of chromosome 8 in the mother of the two boys and in her father. We judge this chromosome abnormality irrelevant to Norrie's disease though it was present in the older boy. There are several families in the records of the Medical

Fig. 1 Family trees of families A and B. In both families there is a sibship of two males with the ocular manifestations of Norrie's disease but no previously affected generation within the memory of accessible relatives. The first affected child in A was mentally and physically retarded while the second child was probably mentally retarded and died aged 9 months of 'sudden infant death syndrome'. Support for the diagnosis of Norrie's disease in the first child in B is his sensorineural deafness. □ = Male. ○ = Female. ◇ = persons of either sex to the total shown by the adjacent number. ■ = Patients reported on here. Oblique stroke = person dead. d-infancy = died in infancy. Arrow = proband. >20 Means that the total number of children from these three individuals included in the bracket numbered more than 20.



Research Council's Clinical and Population Cytogenetics Unit with this chromosome abnormality but no abnormal clinical symptoms or signs.

FAMILY B

Case B1

The first born was a male. (Fig. 1) Bilateral white masses behind clear lenses in small eyes were seen at examination under anaesthesia elsewhere. No further details are available, except that no indication of a possible hereditary cause seems to have been given to the parents. His birth weight was 4.90 kg and occipitofrontal circumference 37.5 cm. An audiogram at the age of 6 years showed early signs of sensorineural deafness (as well as the coexistence of one perforated ear drum). The boy, now aged 8 years, has a hearing aid. These findings support a diagnosis of Norrie's disease. His mental development is normal.

Case B2

The second pregnancy tragically resulted in another male with exactly the same disease. This was a full-term pregnancy, his birth weight being 4.3 kg. His occipitofrontal circumference was 36.4 cm.

The second boy has not had an audiogram done. At age 6 years he is mentally normal. The children were judged too young for venepuncture to allow chromosome studies to be done.

The parents, who were not consanguineous, were counselled after the birth of the second blind boy that the mother was presumptively a carrier of an abnormal X-linked recessive gene causing Norrie's disease, though autosomal recessive non-attachment of retina was definitely possible. They decided against any further pregnancies, and the mother has been sterilized.

Mutation rate for Norrie's disease

Although we favour the diagnosis of Norrie's disease in these two sibships of two males each, there are reservations. The main one is that in neither pedigree is there an affected male on the mother's side of the family. It is theoretically possible, but unlikely, that a forgotten affected male exists far back in both families. The very unlikely possibility exists in all cases of an autosomal recessive congenital non-attachment of the retina syndrome, chance dictating that only males, not females, are affected. However, we much prefer the diagnosis of Norrie's disease, especially because of the mental retardation in both cases in one family (A) and the sensorineural deafness in one of the other sibship (B). We postulate a mutation in the germ cells of one of the maternal grandparents such that the mother is a carrier of the

mutant gene which will be present in half her ova. This mutation will affect all her somatic cells also, but there is no evidence in published families of the existence of a mild form of Norrie's disease in carrier females, as might be expected from the Lyon principle. Alternatively a new mutation could have occurred in one of the ancestors of the maternal grandmother which by chance had not been manifested by the birth of an affected male in a previous generation. It is also a remote possibility that a germline mutation has occurred in the mothers of the boys. (At the stage of a singleton affected boy, a mutation in him could be the explanation.)

We have previously reported another sporadic sibship of two males as having 'congenital hereditary non-attachment of retina'¹⁴ and before that a sporadic brother and sister with the same disease.¹⁷ We remain confident of the autosomal recessive diagnosis in the latter sibship because of the different sexes of the two affected children. However, the two sibships described in the present paper have altered our personal prior probabilities such that we are more doubtful of the diagnosis in the former sibship.¹⁴ Actually in that report¹⁴ we calculated that an X-linked recessive disease was seven times more likely than an autosomal recessive disease: however, we placed considerable weight at the time on the absence of mental retardation and deafness as contraindicating Norrie's disease.

We now think it likely that a mutation has occurred in the gene for Norrie's disease (if it is a single-gene disease) in the germ cells of one of the maternal grandparents in both the families reported here, and so we can calculate a maximum estimate of the mutation rate. Inquiries from the Blind Welfare Services and the ophthalmologist to the School Health Service and Blind School in Glasgow (the only other Blind School in Scotland) have not revealed any other cases of Norrie's disease in Scotland. However, undiagnosed cases may exist, especially in institutions for the mentally retarded. In any case our postulated two new mutations in females will be an underestimate of the true number of new mutant females because (a) some new mutants will be too young to have had any children; (b) some new mutants may by chance have had no children, or only females, or only normal male children.

We propose to restrict the calculation to concern only women between 18 and 45 years of age in Scotland. From the 1981 *Annual Report* of the Registrar General for Scotland¹⁸ we estimate that 25.9% of women of this age in Scotland are unmarried and 74.1% are, or have been, married.

Family size is important. Given that there is a 25% (1 in 4) risk of an affected child in the case of a woman 'carrying' an abnormal gene on one X chromosome,

for a woman with a family of size s the probability that she would have at least one affected child is $1-(0.75)^s$. The proportion of all carrier women who will have an affected child is therefore $\sum P_s (1-(0.75)^s)$.

⁵ Where P_s is the proportion of women with family size s . Estimates of P_s for married women in Britain aged 18–45 years were obtained from the 1981 census. Substituting in the above formula, we estimated the overall proportion of married mutant carriers who would be ascertained by the birth of an affected child to be 0.3515.

If we assume that single women have had no children, the proportion of new mutant carriers ascertained among all women age 18 to 45 is: $(0.259)(0.0) + (0.741)(0.3515) = 0.2605$

Therefore the actual number of new mutant carriers is

$$\frac{\text{observed}}{0.2605} = \frac{2.0}{0.2605} = 7.6775.$$

Now the total number of women aged 18 to 45 resident in Scotland is 978 740.

Therefore the number of mutant genes carried by these women as a proportion of the total is

$$\frac{7.6775}{2 \times 978\,740} = 3.9 \times 10^{-6}.$$

Therefore the mutation rate per chromosome is 3.9×10^{-6} .

Pathological report (case A2)

The eyes and brain had been removed and fixed in formol saline within 24 hours of death.

OCULAR PATHOLOGY

Macroscopic examination

The right eye measured 18×18×10 mm, the right cornea 10×9 mm with 3 mm of optic nerve attached; the left eye 18×17×17 mm, and the left cornea 9×8 mm with 5 mm of optic nerve.

The findings in both eyes were very similar and will be considered together (but where differences occurred they will be mentioned).

The cornea was clear and the anterior chamber very shallow. The pupil was small, eccentrically placed and with marked ectropion uvae. There was leucocoria. The eyes were opened horizontally, revealing total funnel-shaped retinal detachment with subretinal coagulum. The retina was yellowish and incorporated a scattering of blood and pigment.

Microscopic examination

Both eyes were serially sectioned and were stained with haematoxylin and eosin, periodic acid Schiff, Perl's, Masson's, Bodian, and Loyez stains.

The corneal epithelium was uniformly thick, with

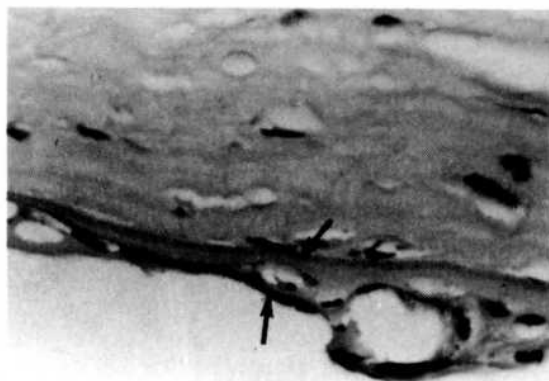


Fig. 2 Corneal endothelium showing irregular heaping up of cells with reduplication of Descemet's membrane (arrows). (H and E, ×320).

numerous mitotic figures within it. Bowman's membrane was prominent and intact, while the stroma was of normal thickness and unvascularised. Descemet's membrane was uniformly present except in one very small area axially in each eye, where there was also no endothelium; this may represent a mild degree of Peter's anomaly. The remainder of the axial endothelium was greatly attenuated, with only a rim of normal endothelial cells at the periphery. The axial endothelial cells contained pigment granules. There was an area in the axial region of the right eye where the endothelium formed two layers of spindle-shaped cells with reduplication of Descemet's membrane (Fig. 2).

Extensive anterior synechiae occupied the area from the mid-zone of the iris to the pupillary margin (Fig. 3), with total posterior synechiae covering the

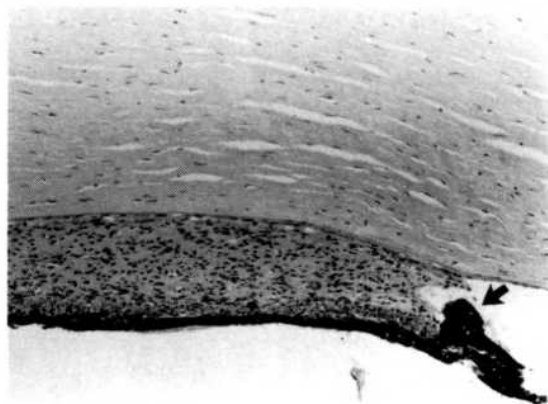


Fig. 3 Extensive anterior synechiae and poliferation of iris pigment at pupil margin (arrow). (H and E, ×78).

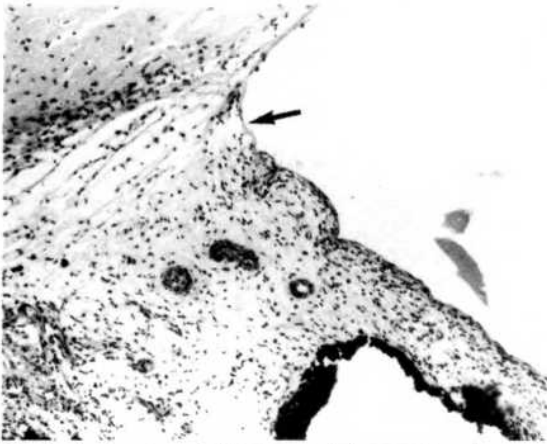


Fig. 4 Drainage angle showing goniodysgenesis and strands of material bridging angle (arrow). (H and E, $\times 78$).

entire lens surface. The drainage angles were open in some areas but closed in others by iris strands bridging the angle. Descemet's membrane ended in the region of

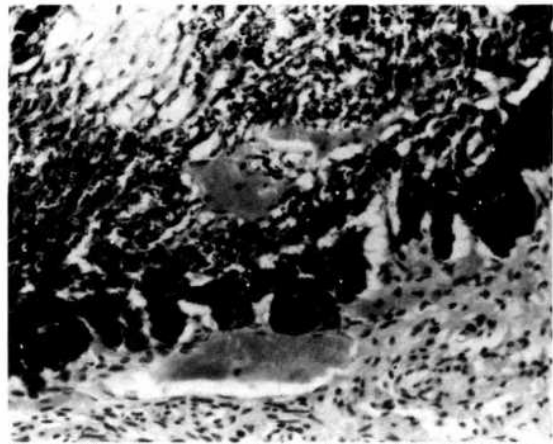


Fig. 5 Hyperplasia and spindle cell metaplasia of pigment epithelium of ciliary processes. (H and E, $\times 200$).

the iris strands, further anteriorly than normal. There was an increased density of tissue in the region of the trabecular meshwork with the scleral roll extending

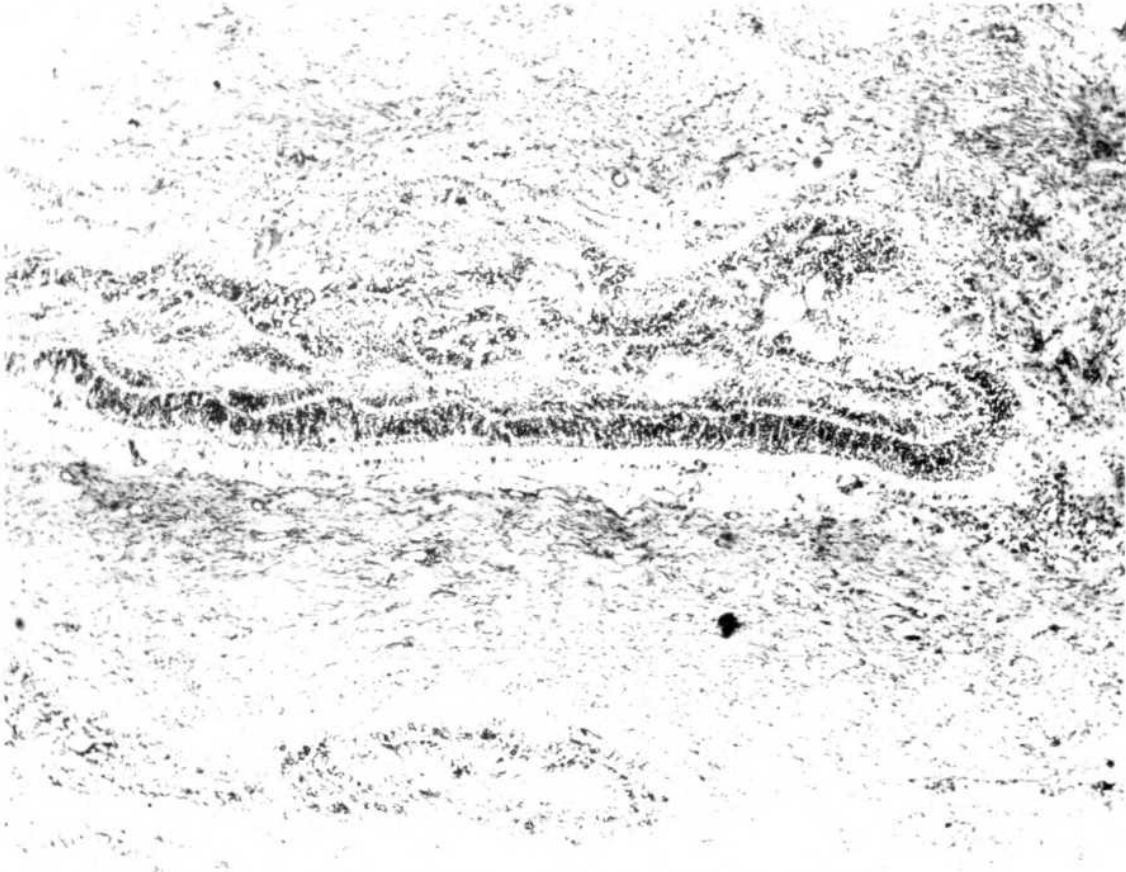


Fig. 6 Folded retina showing some areas of differentiation and others of gliosis. (H and E, $\times 64$).

further anteriorly than normal, indicating a degree of goniodysgenesis (Fig. 4). There was a very delicate neovascular membrane over the iris surface with a persistent pupillary membrane. The pigment epithelium of the iris showed ectropion, with considerable proliferation of pigment over the anterior surface of the iris. The thickness of the iris was variable, with some parts being abnormally thin. The cellularity of the stroma was unremarkable.

The ciliary processes were drawn forward and elongated, but not to the degree found in persistent hyperplastic vitreous. There was very dense pigmentation of the epithelium, and both eyes showed nodular areas of spindle cell metaplasia and hyperplasia of the pigment epithelium in the posterior part of the pars plicata (Fig. 5).

The lens was displaced anteriorly. The capsule and epithelium were intact, and there was no evidence of cataract formation.

The retina was lying in a tightly folded mass behind the lens (Fig. 6) and was attached only at the optic nerve head. Moderately well differentiated photoreceptor nuclei, bipolar cell nuclei, and ganglion cells were identifiable, being arranged in recognisable layers.

Some areas were more dysplastic with rosette formation, and in particular the peripheral retina was less well differentiated, with the extreme periphery being represented by a simple columnar epithelium. The pars plana was totally detached. There had been

recent as well as old haemorrhage into the retina, which contained blood haemosiderin and clumps of melanin. There was a marked glial component in the retina. The retinal pigment epithelium showed two patterns of proliferation. At the periphery it formed focal budding patterns with cells free in the subretinal fluid, whereas posteriorly it formed a uniform two-layered columnar epithelium. The subretinal space was filled with eosinophilic material containing a few retinal pigment epithelial cells and pigment laden macrophages.

There were a preretinal vascular membrane and an anterior condensation of the vitreous. Some large vessels in the vitreous in the cone of the detachment may represent remnants of a persistent hyaloid system, though all were thin-walled.

The vessels in all the layers of the choroid were patent. There was marked thickening of the sclera, but no specific abnormality.

The optic nerve was thin, with posterior bowing of the lamina cribrosa, which was the anterior extent of myelination. There was a very marked reduction in the number of nerve axons, with a more marked loss at the outer rim of the nerve and at the superior and inferior extremes (Fig. 7).

EXTRA-OCULAR TISSUES

These were unremarkable. Examination of the brain showed no abnormality other than thinning of the optic nerves.

Discussion

CLINICAL AND GENETICAL

We consider it unlikely that these sibships are both examples of the autosomal recessive disease 'congenital non-attachment of retina'^{16 17 19-21} rather than Norrie's disease. We postulate a reasonable chance that a mutation has occurred in the *X* chromosomes of a germ cell of a maternal grandparent in our two sibships of two males each. The hypothesised mutation might even have occurred further up the female line with diminishing likelihood, since affected males would be expected to be remembered for several generations.

The possibility that the main alternative diagnosis is congenital non-attachment of retina would imply that chance has dictated the coincidence that all four cases in the present report merely happen to be in males, that is, that affected females might have been born instead (which would effectively exclude Norrie's disease). Non-ophthalmological points in favour of Norrie's disease exist in both families: the development retardation and sudden death²² in case A2 and mental and physical retardation in A1, and a much stronger support in case B1, namely deafness.²³

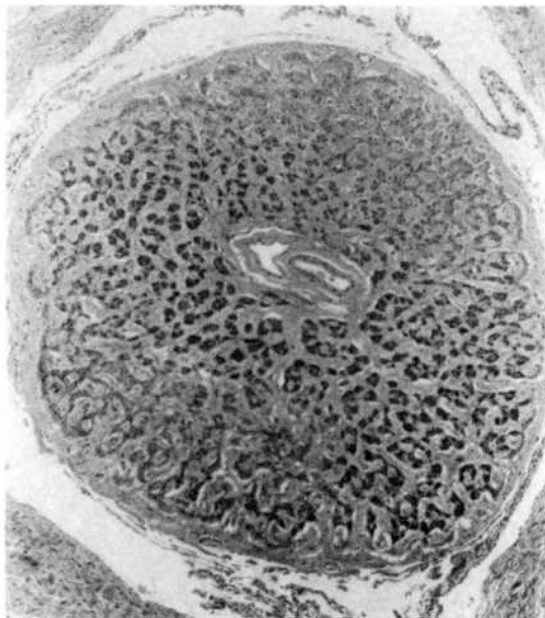


Fig. 7 Optic nerve, with more marked axonal atrophy at superior and inferior margins. (H and E, $\times 40$).

However, these additional handicaps are by no means always present in Norrie's disease, which may in turn suggest that Norrie's disease contains several different variants—as would be expected from the variability of the biochemical lesion of the DNA in any hereditary disease. Even if linkage of a specific allele with the Norrie's disease gene were found consistently in the two families,²⁴ that would not constitute support for the diagnosis of Norrie's disease; conversely the absence of linkage would not contraindicate Norrie's disease.

An autosomal recessive total detachment of retina ('retinal dysplasia') with microphthalmos and nystagmus occurs in Bedlington and Sealyham terriers and Labrador retrievers.²⁵⁻²⁸

In the differential diagnosis we would consider but exclude persistent hyperplastic primary vitreous

because it has never been recorded in sibships so far as we know, and there are claims for bilateral involvement in only three cases.^{29,30} Retinopathy of prematurity can be confidently ruled out. The absence of systemic abnormalities is evidence against 'retinal dysplasia'.^{31,32} That name was introduced by Reese and Straatsma in 1958³² in their description of 44 cases of which 27 had only ocular disease. The absence of abnormalities of skin colour excludes incontinentia pigmenti, and the absence of skeletal abnormalities excludes dysplasia spondyloepiphysaria congenita^{33,34} and Sraux's syndrome.³⁵

It seems likely that, in the pathological evolution of Norrie's disease in intrauterine life, the retina has never been 'attached' (that is, the inner layer of the optic cup has not achieved contact with the outer

Table 1 Summary of literature on histopathology of Norrie's disease

	No. of cases	Age at enucleation	Anterior segment	Posterior segment	Neuro-pathology	Comment
Heine 1925 ¹	2	4 years *4 months	Anterior synechiae Ectropion uvae	Ossification of choroid	—	Early phthisis
Whitnall, Norman 1940 ³⁶	1	17 years	Anterior synechiae, ectropion uvae	Undifferentiated retina, ossification	Yes	Phthisis bulbi
Wilson 1949 ⁵	3	*1 month	Iridocorneal adhesion, hypertrophic ciliary processes	Undifferentiated retina		
		*3 months	Anterior synechiae, ectropion uvae	Moderate differentiation		Phthisis bulbi
		5 years	Anterior synechiae	Moderate differentiation of retina with retrolental haemorrhage and subretinal haemorrhage		Glaucoma
Reichel 1960 ²²	2	4–5 months R:1 month L:6 months	No details	Retinal detachment with haemorrhage	Yes	Phthisis bulbi, glaucoma
Warburg 1961 ⁴	1	*8 months	Goniodysgenesis, ciliary epithelial hyperplasia		Yes	Early phthisis
Blodi, Hunter 1969 ⁹	6	14 years	Synechiae	Calcified choroid		Phthisis bulbi
		*3½ months	Shallow anterior chamber	Retinal haemorrhage		
		*1½ months	Synechiae	Retinal haemorrhage		
		5 years	Synechiae	Calcified choroid		Phthisis bulbi
		3 months	Synechiae	Retinal haemorrhage		
		2½ months	Total anterior synechiae	Retinal haemorrhage		
		*1 month	Gonidysgenesis, ectropion uvae, long ciliary processes	Moderate dysplasia		
Townes, Roca 1973 ¹²	1	3½ years	Advanced disorganisation			Phthisis
Apple, Fishman, Goldberg 1974 ³⁸	1	11 years	Anterior synechiae	Gliotic retina		Phthisis
		3 months		Dysplasia		Vitrectomy specimen
Warburg 1975 ¹⁵	3	18 years	Long ciliary process	Retinal haemorrhage		?Acquired retinal detachment
		*5 months	Synechiae, ciliary epithelial hyperplasia	Dysplasia		
		15 years	Ciliary epithelial hyperplasia, long ciliary process, ectropion uvae, synechiae	Persistent hyaloid artery, calcified choroid		Phthisis

* Adequate histology possible.

layer). A study of fetuses at different stages of development in the Sealyham terrier and other dogs^{25,26} would be instructive and might well cast some light on the (biochemical) cause of the disease—possibly a defect in the pumping mechanism of the retinal pigment epithelium or a defect in the hyaluronic acid between the pigment epithelium and the layer of rods and cones.

One biopsy report¹⁹ showed normal retinal and connective tissue. This was taken during an attempt at surgical correction which failed, but the author suggests that an operation in the earlier stages might be successful.

PATHOLOGY

Although 21 cases have had histological findings reported, most had phthisis bulbi. They are summarised in Table 1, but the eight with distinguishable features have been indicated by asterisks.

Non-attachment of the retina is the major pathological as well as clinical finding. That description is used in preference to 'detachment' because of our suspicion that the inner layer of the optic cup never achieved contact with the outer layer in intrauterine life. The dysplasia of the retina may be due to lack of stimulation by the pigment epithelium to differentiate, and conversely a similar explanation may apply to the abnormal stratification of the pigment epithelium.²⁷ The absence of secondary vitreous suggests that the inner layer never achieved attachment because its formation is induced by the fusion of neuroretina to pigment epithelium.⁷ Significant in this context is the association between defects in the formation of the optic cup and microphthalmos, which is also part of Norrie's disease. However, non-attachment of retina might be expected to produce more severe microphthalmos than is usually present at birth in Norrie's disease; these eyes shrink subsequently.⁶

The association between microphthalmos and non-attachment of retina suggests a similar explanation for malformations of the anterior segment which have been found in the few cases in which organised structures remained: see Table 1, where it will be seen that our observations correspond with those of others—goniodysgenesis, iridocorneal adhesion with ectropion uveae, a disturbance of corneal endothelium, and persistence of the pupillary membrane.

There are only three cases in which neuropathological examination was recorded. Two^{4,28} showed thinning of the optic tracts and a reduction in cellularity of the lateral geniculate bodies. A third previously reported case²⁹ showed no morphological abnormality of the brain at necropsy. Neuropathological examination of the case reported here showed only attenuated optic nerves.

Note added in proof. Clarke's may be the first briefly recorded family,¹⁴ followed by that of Ash in 1922,⁴⁰ extended by Fraser Roberts in 1937⁴¹ (see Waardenburg *et al.*² for other early references).

We are grateful to Dr NL Stokoe, consultant ophthalmic surgeon at the Royal Blind School, Edinburgh, for permission to see the pupils in the Blind School and their relatives; to Professor WR Lee, of the Department of Pathology, Western Infirmary, Glasgow, for discussions of the histopathology, and to Mr JAW Ralston for preparation of the histopathological specimens.

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Arabic reading types

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SUMMARY Greatly needed Arabic reading types for testing near visual acuity are suggested. They are based on reading types adopted by the Faculty of Ophthalmologists of the United Kingdom.

Testing near visual acuity has its place in the assessing of the macular function and prescribing a suitable addition for presbyopia. Some eye diseases affect reading acuity to a great extent such as posterior subcapsular cataract.¹ Hence its testing is an indispensable part of ophthalmic examination.

The first scientific attempt to test near visual acuity was made by Snellen in 1868,² who applied to the test the same principle as he applied to his distance types. Each letter is made as a square subtending an angle of 5' at the ordinary reading distance.¹ The unfamiliar configuration of letters of that construction, however, is not reproduced in ordinary printer's founts.³

Jaeger's suggestions^{2,3} found more general acceptance because they consisted in ordinary printer's founts of that time. Jaeger's types persisted for a long time, though their uniformity was entirely lost mainly because the original founts from which the types were produced became obsolete.⁴

To overcome this difficulty the British Faculty of Ophthalmologists put forward the suggestions⁴ and then recommendations for standardisation⁵ of reading types. Times Roman type face is used with standard spacing. (Times refers to the print used by *The Times* newspaper.) The notation was based on the printer's point system, where specimens of printed materials are given in sizes of 5 pt, 6 pt, 8 pt, etc. (a point stands for 1/72 inch (0.35 mm) and indicates the size of the block on which individual letters are cast;² 5 point type is one in which each letter is cast on a block 5/72 inch (1.76 mm) tall. This test proved its adequacy for the examination of near visual acuity for more than 30 years.

Arabic reading types

Arabic test types for distance visual acuity were standardised in 1968 by Emarah.⁶ Based on Snellen's

concept, they are inadequate for testing reading acuity for the same reason as made the Snellen reading test unpopular, namely the unusual configuration of the letters. Experience has shown that there is a need for suitable Arabic reading types for near visual acuity. Firstly, there are many people who read Arabic but not English. Secondly, there is a difference in size between Arabic and English letter blocks for the same size of printed material.⁷ Arabic letters are larger by 1 to 2 points than the same size in English letters owing to the frequency of punctuation over or under the line and the frequency of ascenders or descenders in Arabic print.⁸ The smallest available Arabic print is 6 point, which is comparable to 4.5 point in English print.^{7*}

The following suggestions are made for the standardisation of Arabic reading types, and an example is provided in Fig. 1.

(1) The traditional monotype computer print type face should be used, as it is the commonest print in use in modern Arabic newspapers.

(2) 'Dark' monotype should be used for better contrast as opposed to 'light' monotype.

(3) The sizes of print recommended are 6 pt, 7 pt, 8 pt, 10 pt, 12 pt, 14 pt, 18 pt, 24 pt, 36 pt, and 48 pt, starting with the smallest size print.

(4) Suitable passages should be selected from Arabic literature and a different passage used for each print size. Isolated words can be used to eliminate the possibility of guessing the reading material from its general sense. In addition pieces from well known printed material can be provided in different sizes like a telephone directory.

(5) The test can be printed on a single sheet or in booklet of durable and cleanable material made of plastic or varnished white card.

(6) Near vision is recorded as the smallest type which the patient can comfortably read together with a note of the approximate distance at which the card is held, such as 'A 8, 30 cm', meaning a reading print size of 8 pt, in Arabic, at distance of 30 cm.

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- ٦ بنط
احذر الرجل رجلا ليده القماء فقال له الا احسن القماء ولا انا قاله قال الرجل بهك ثلاث خصال الله ذرف والذرف مع صاحبه من الله طرفة حلم يحكمه من الصالحين من لم يحل قال
عنه وان رحل تدور في امرك وس ذوق كل صوته واما الله لم يحكم الله من الله به اقول القماء لما وحدوا في سخطا
- ٧ بنط
يقال للحيلة المصمم جلفه لا تتوكل على الغنى وما قال في الامم ذوق ليا وهو لاس الخفاء الصالحين وفتح لغية فروح عمودية ومنية باليك ومنية الرطو والقمة الاخرين
ومصر والمزيجان وديار صيحة ولوبيبة واستطفت ليلي سبي ولغية لغير ولغية ليام وخطف لغيره بين وفاني بهات
- ٨ بنط
الحصل فيه به في حياتك هو الصلح من عدوك والصبر عن غايصة حصيلك والاحلاس لصديقك والقدرة الحسنة لطفلك والاحسان لواتيك
والاحرام لفسلك والهمة ختمك الناس .
- ٩ بنط
في الحديث:
ثلاث منجيات: خشية الله في السر والعلانية والقصد في الفقر والغنى وكلمة الحق في الغضب والرضى. وثلاث
مهلكات: شح مطاع وهوى معبوع واهجاب المرء بنفسه .
- ١٢ بنط
الكتاب عصارة الفكر النير والرأي السديد وذوب الفؤاد ومخلاصة الوجدان الحلي فلا الذهب بأثمن
من الكتاب ولا الثروة ولا الغنى بابقى واحمد منه .
- ١٤ بنط
قال ابو عبد الله المغربي:
اعظم الناس ذلا فقير داهن غنيا او تواضع له واعظم الخلق عزا غني تدلل للفقراء
وحفظ حرمتهم .
- ١٨ بنط
قال حكيم ساخر: رأيت اكثر الذين يرتقون الى المجد يسرون على
اكتاف اصدقائهم ولما على جماجم اعدائهم .
- ٢٤ بنط
قال ملك حكيم: لا ملك الا بالجنود ولا جنود الا
بالمال ولا مال الا بالرعية ولا رعية الا بالعدل .
- ٣٦ بنط
الويل للخزف إن سقط على
الصخر والويل له إن سقط
الصخر عليه .

Fig. 1 Different sizes of Arabic printing in a suggested set of Arabic reading types for near vision.

I am grateful to Mr Gazi Harak and his staff in *Al-Watan* newspaper for their technical assistance.

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The Dunlop test and reading in primary school children

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SUMMARY Using the Dunlop synoptophore test we have examined the reliability of vergence control for small fusion targets in 753 primary school children aged 7–11, and we have compared these results with the reading performance of 451 of them. 30% of the total sample of children had unstable responses in the Dunlop test. The proportion decreased with age, ranging from 49% of 5-year-olds to only 11% of 10-year-olds. The reading of children who had developed accurate vergence control was on average 6.3 months in advance of those who had not. Those with unstable Dunlop test responses were much more likely to be backward or low normal readers than children with stable responses. We conclude that in experienced hands the Dunlop test is a useful indicator of the development of vergence control and that immaturity of vergence control may contribute to children's reading problems.

We have recently put forward the hypothesis¹ that many children with specific reading difficulties (developmental dyslexics) may suffer a disorder of binocular vergence control when they inspect small fusional stimuli. Their poor vergence control may lead them to mislocate, missequence, and misorientate letters when they try to read small print. We have been using the Dunlop synoptophore test of vergence stability² to investigate such children with reading difficulties. In 1982 we reported that between half and two-thirds of dyslexic children had abnormal responses in this test,³ whereas very few normal readers suffered these problems. However, Newman *et al.*⁴ have recently found in a sample of 298 unselected primary school children that there were almost as many normal as backward readers who gave abnormal responses in the Dunlop test. Their high proportion of 'false positives' casts doubt on the reliability of this test for helping with the management of children with reading problems.

Over the past few years we also have been examining a large number of unselected primary school children in order to determine the incidence of abnormal responses in the Dunlop test in a 'normal' population. We obtained reading age information about these children after the orthoptic examinations

had been completed, so that, like Newman *et al.*, we could compare the Dunlop test results with reading performance. However, we found fewer false positives than Newman *et al.*, and we confirmed that many more backward than normal readers have abnormal responses in the Dunlop test. Preliminary reports of some of these findings have already been published.^{5–7}

Material and methods

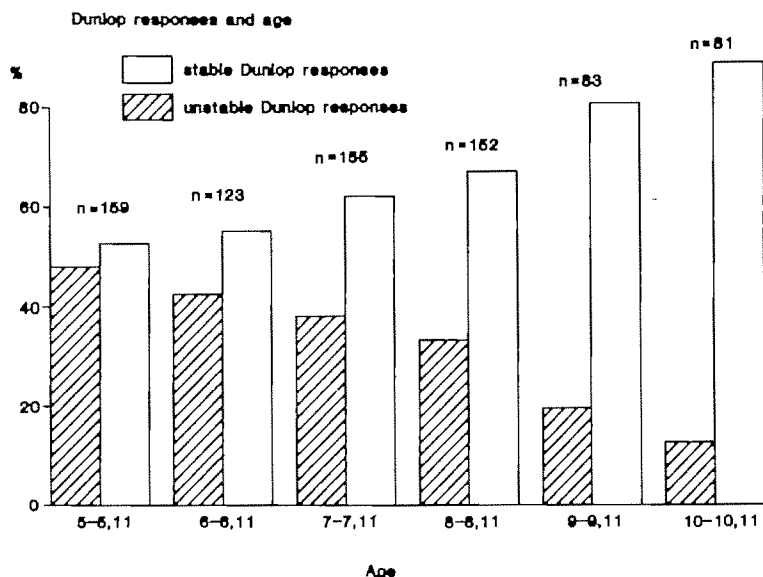
SUBJECTS

We visited 11 primary schools in widely different neighbourhoods around Reading which had kindly agreed to participate in these studies. In all, 753 children aged between 5 and 11 were examined. Each child was given a brief orthoptic examination to exclude ophthalmological disorders. No child with significant refractive error, squint, or ocular pathology is included in this report. Then the Dunlop test was administered 10 times. The procedure was similar to that followed in our first study,³ and also to that followed by Newman *et al.*⁴

In the test the child viewed two almost identical macular sized fusion scenes through a synoptophore. The slide viewed by the right eye had a house with a small pole to the left of the front door, while the left eye saw a house with a large pole to the right of the door. The angle of the synoptophore tubes was

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Fig. 1 The proportions of children at different ages having stable or unstable Dunlop test responses. Whereas 48% of 5 year olds had unstable responses, only 11% of 10 year olds did.



adjusted until the two scenes fused. Then the orthoptist slowly abducted the synoptophore tubes (at 1–2°/s), and the subjects attempted to diverge their eyes to maintain fusion. When children understand clearly what they have to do, most gain a clear impression that one of the poles seems to move towards the door during this procedure. After about 5° divergence (2½° for each eye) diplopia intervenes. On repeating the test 10 times, the slides being changed over frequently to try to prevent guessing, most children report movement of the pole on the same side on every trial. However, some children give inconsistent reports in the test. Their eyes did not diverge adequately, one or other of the poles seeming to disappear temporarily, and diplopia occurred much earlier after only 1° or 2° abduction of the tubes. The children reported that both the poles appeared to move either simultaneously or on successive occasions. If a child reported that both poles appeared to move during the test either simultaneously or successively on three or more trials, he/she was said to have unstable Dunlop test responses, a result denoting poor vergence control under these conditions.

For 451 of the children we could obtain reading ages from their teachers (Shonell single word, Neale or NFER group tests) together with some intelligence quotient (IQ) data. Although combining the results of different reading tests is undesirable, it is not likely to have caused systematic errors. We had individual IQ scores for only a few children, but all the children whose reading results we have included had IQs above 90 by class-administered tests.

Results

Of our total sample of 753 children aged 5–11 years 263 (35%) were found to have unstable responses in the Dunlop test. But the proportion of children with stable responses increased year by year. Fig. 1 shows that, whereas only 52% of 5–6 year olds had gained stable responses, nearly 90% of 10–11 year olds had done so. Thus among 7–11 year old children taken as a group we found that 27% showed unstable vergence control in the Dunlop test. Newman *et al.* found 56% of 7–11 year olds to have abnormal Dunlop responses.⁴

We found that those of the 6–11 year old children who had achieved accurate vergence control were on average 6.3 months better at reading than their peers with unstable control. Reading ages for the 5 year olds were not available. The difference between stable and unstable groups was highly significant statistically ($p < 0.01$). A similar trend may be seen in some of Newman *et al.*'s results, but the statistical significance of this difference was not calculated.

In Fig. 2 the proportion of 6–11 year olds with stable or unstable Dunlop test responses is plotted as a function of quartile differences between reading and chronological age in the same way as Newman *et al.* presented their results.⁴ 44% of those whose reading was more than 18 months behind their chronological age (backward readers) had unstable responses in the Dunlop test, as did 40% of low normal readers, compared with 26% of high normal and only 14% of advanced readers (reading age more than 18 months ahead of chronological age). The

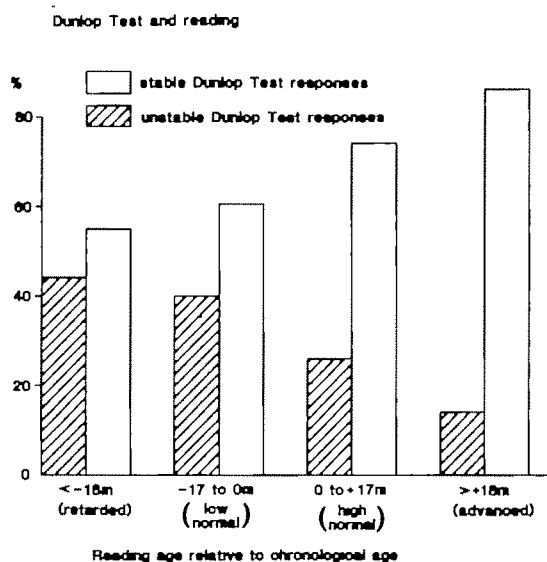


Fig. 2 The proportions of children of different reading levels relative to their age having stable or unstable Dunlop test responses.

differences between the groups were highly significant ($\chi^2=14.98$; $df=3$; $p<0.005$). The same trends may be seen in Newman *et al.*'s results, but their differences were not statistically significant.⁴

Discussion

These results support the conclusions of our earlier study¹ that the Dunlop test is useful in the investigation of children with reading disorders. In the sample reported here nearly half the children whose reading was more than 18 months behind their chronological age were found to have unstable responses in the Dunlop test compared with only 14% of advanced readers and 24% of all the children whose reading was ahead of their age. These differences were highly significant. Likewise the reading of those with unstable Dunlop test responses was on average over six months behind that of their peers with stable control.

Nevertheless in this study we found many more 'normal' readers with unstable vergence control than we did in 1982. There are a number of reasons for this. First, we chose exceptionally good readers as our controls in our earlier study. Their average reading age was over two years ahead of their chronological age. The figures reported here imply that less than 10% of such advanced readers would be expected to have abnormal Dunlop test responses. In addition the backward readers in our earlier study were much worse than most of the children reported

here. Their reading was two to three years behind their chronological age; our present figures suggest that over 60% of such highly retarded readers would have abnormal Dunlop test responses.

Another way in which the results reported here differ from those of our previous study is that then the reading age of all the 160 children was measured by a single test, the Neale analysis of reading accuracy. However, we did not have the resources to assess the reading ages of all the children reported in the present study ourselves. Different reading tests were employed by the teachers of different groups of children. This is bound to have reduced the accuracy of the reading assessments. Adding 'noise' in this way, however, is likely to have reduced differences between the groups rather than increased them. Moreover it is unlikely to explain the systematic differences which we observed in the reading ability of children with stable as compared with those with unstable Dunlop test responses.

A most important additional reason why we observed more normal readers with abnormal Dunlop test responses among these unselected primary school children than in our earlier study is because we examined older children then. The average age of the children in our 1982 study was 10 years 1 month, whereas in our present sample (excluding the 5 year olds, for whom no reading ages were available) it was just over 7 years. We show here (Fig. 1) that the proportion of abnormal responses decreases with the age of the children. Whereas only 10% of 10 year olds had unstable responses on the Dunlop test, overall 30% of our sample of 6-11 year olds showed poor vergence control. But the reading of the majority of children with unstable responses was low normal rather than seriously retarded. About a third of the 6-11 year old children we studied had unstable visuomotor control, yet the reading of most of these was within normal limits. This suggests that, although the normal development of visuomotor control was somewhat delayed in these children, most of them were not irreversibly affected and would probably catch up. But there is a residue of 5-10% of children whose acquisition of stable vergence was so delayed as possibly to lead to significant problems.

In our earlier study we suggested that children who had not achieved stable vergence control by the age of 10 may account for between half and two-thirds of children with specific reading retardation, or dyslexia. However, because we had inadequate IQ information in this study, we have not been able to relate reading to IQ, only to chronological age. Hence we cannot with any certainty identify any of the children in this study as truly dyslexic. If we had been able to express the children's reading as a

function of their IQ more of those with abnormal Dunlop test responses might have been found to be poor readers relative to their IQ, and more children with normal responses but lower IQ might have been classified as advanced readers in relation to their IQ.

Although the same trends as we report here may be seen in some of the results of Newman *et al.*, they found many more normal and advanced readers with abnormal Dunlop test responses⁴ than we did. So the differences between their groups were not statistically significant. Newman *et al.* suggested that in our first study we may have been biased by knowing that our clinic referrals were likely to have been mainly reading retarded while our primary school children were mostly normal readers. However, in the present study we examined an unselected group of children in their schools without even such general prior knowledge of their reading, yet found that those with abnormal Dunlop test responses were very significantly overrepresented among the poorer readers.

We have only just begun to appreciate the unreliability of this test in inexperienced hands. It relies heavily on the ability of young children to concentrate on an unfamiliar and complex perceptuomotor task. Accordingly the person administering it needs to be highly experienced with working with children and interpreting their reactions, to make sure that they have really understood the task and are not merely trying to guess as a result of their natural desire to please. We have recently shown⁸ that we can assess a child's vergence control objectively by recording the movements of each eye during the Dunlop or other synoptophore vergence tests. Such recordings provide a more reliable indicator of visuomotor abnormalities in reading by retarded children. They are also more satisfactory for monitoring procedures aimed at improving vergence control, such as monocular occlusion.¹

It has been suggested that low normal and retarded readers have unstable responses in the Dunlop test merely because they find it difficult to understand the test. However, the instructions for the Dunlop test are verbal; they do not involve any reading. Moreover we have shown that whether children have unstable responses in the Dunlop test³ or whether

they respond to monocular occlusion treatment by developing stable visuomotor control¹ is independent of their IQ. Many highly intelligent dyslexics have unstable Dunlop test responses, whereas many children with below average IQs can understand the instructions in the Dunlop test sufficiently well to give stable responses.

It has also been suggested that rather than unstable visuomotor control causing reading difficulties cause and effect are the other way round—that is, children develop reliable vergence control after they have learnt to read. However, we have shown that a reading spurt, if it occurs in dyslexics, always follows acquisition of stable Dunlop test responses and usually cannot proceed without such development of reliable visuomotor control.¹ Thus it seems likely that developing accurate vergence control is a vital prerequisite for learning to read normally. This explains why at all ages those with unstable Dunlop test responses tend to be worse readers than their peers with stable vergence control.

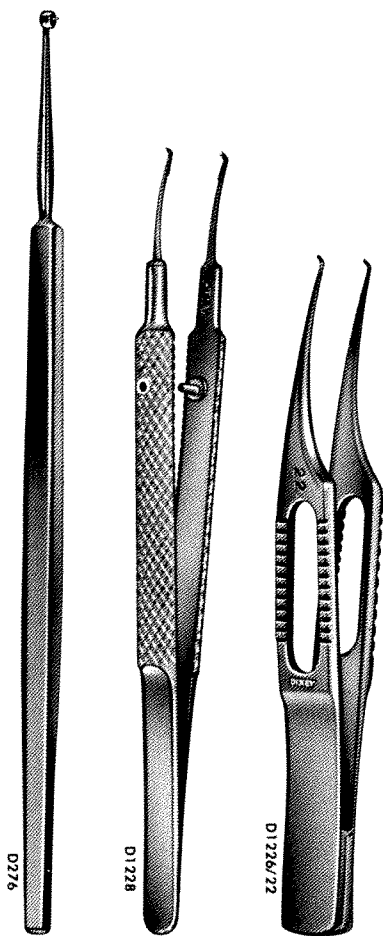
We thank Mr D Brownhill, chief psychologist, Berks Education Department, for his help and support and the Oxford Regional Health Authority for financial assistance.

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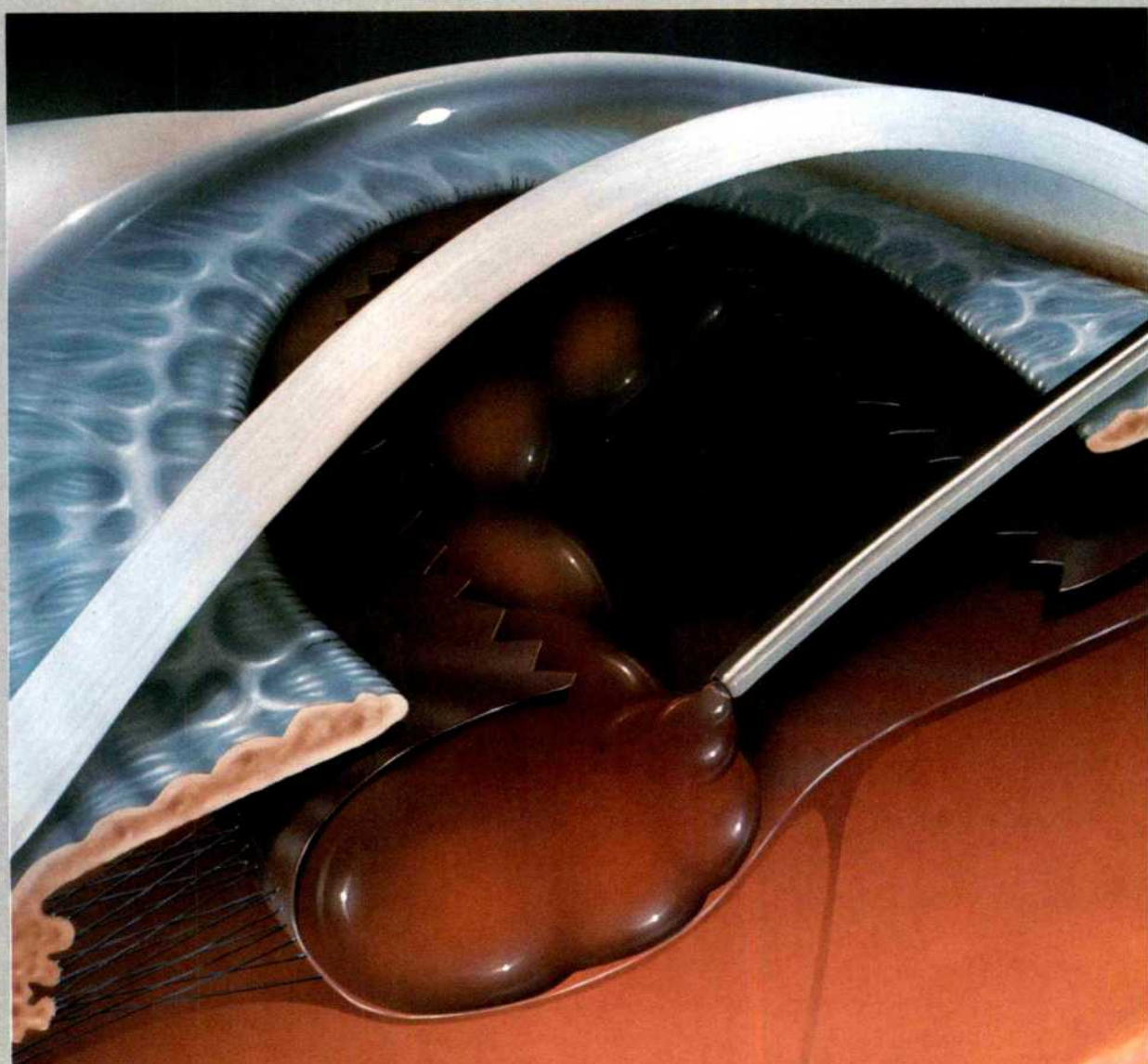
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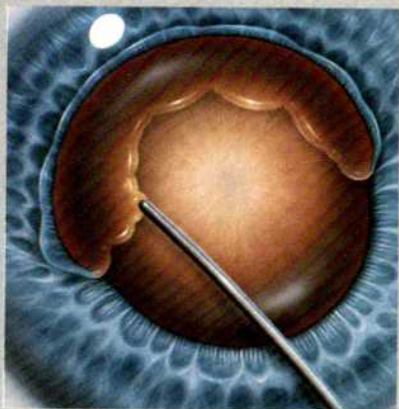


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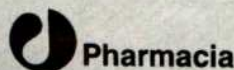
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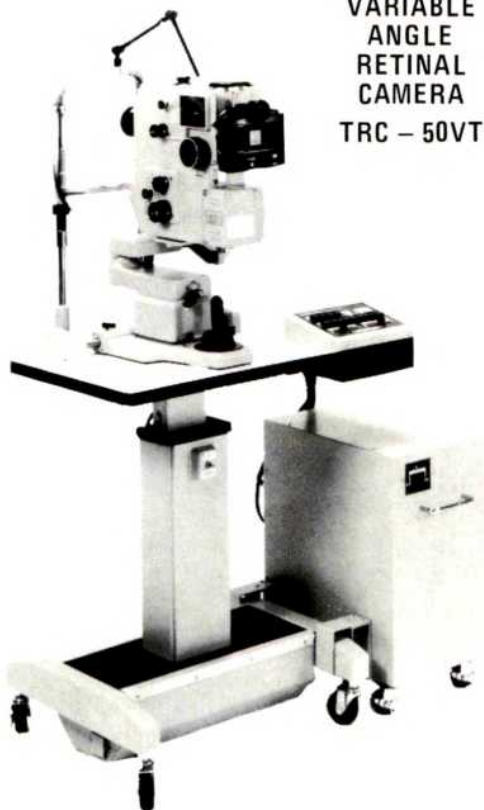
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Freeze frame analysis on high speed cinematography of Nd/YAG laser explosions in ocular tissues

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SUMMARY High speed colour cinematography at 400 frames per second was used to photograph both single and train burst Nd/YAG laser applications in ox eyes at threshold energy levels. Measurements of the extent and speed of particle scatter and tissue distortion from the acoustic transient were made from a sequential freeze frame analysis of the films. Particles were observed to travel over 8 mm from the site of Nd/YAG application 20 milliseconds after a single pulse at initial speeds in excess of 20 km/h. The use of train bursts of pulses was seen to increase the number of particles scattered and project the wavefront of particles further from the point of laser application.

In recent years the use of the Nd/YAG laser has gained wide acceptance in anterior segment surgery.¹ To observe the events occurring immediately following the optical breakdown phenomenon, we filmed the action of the Nd/YAG laser in an ox eye using high speed cinematography. At a film speed of 400 frames per second we observed particulate dispersion and tissue distortions in the first few milliseconds following plasma formation.

Plasma formation and the acoustic transient it generates occur only when the energy applied is at or above a threshold which varies with the molecular composition of the target.² Observation of threshold pulses will therefore give a guide to the minimum effects to be expected during clinical use.

Material and methods

The short pulsed, Q switched Nd/YAG laser photo-disrupter used in this study was a Lasag Sirius Microruptor II.

Fresh ox eyes were mounted so that the helium/neon aiming beams of the laser could focus via the central cornea on the anterior lens capsule and iris respectively. The eyes were maintained in a moist condition for filming by the frequent application of methyl cellulose drops. Contact lenses were not used during the study for laser focusing, as their use would have interfered with filming. Adequate lighting was obtained by condensing a 2 kW tungsten halogen light using a system of lenses.

With the camera running at 400 frames per second predetermined threshold pulses were delivered while the laser aiming beams were focused on the anterior lens capsule (2.4 mJ) and iris (2.9 mJ) just below the pupil margin. A train of five pulses of 2.9 mJ per pulse at 20 millisecond intervals was then applied to the iris. The film was subjected to freeze frame analysis by projecting individual 16 mm frames on to a screen and measurements of particle scatter and tissue displacement were made. These were converted to real values from direct proportional data.

Graphs of particle displacement against time were constructed from the knowledge that the camera shutter opens for 1/1200 second per frame at a film speed of 400 frames per second and is closed for 1/600 second between frames.

Results

In the first frame showing observable events following a threshold pulse of 2.4 mJ applied to the capsule the shockwave had already scattered bubbles and particles 3.78 mm from the target point (Fig. 1). The exact timing of the 12 nanosecond pulse could not be determined even at a film speed of 400 frames per second and could have occurred at any point following the closure of the shutter from the previous frame. The maximum time for the measured initial particle displacement was 1/400 s, indicating a minimum mean particle velocity of 1.5 m/s (5.4 km/h) in the first few milliseconds following plasma formation.

Fig. 2 shows the rapid deceleration in particle



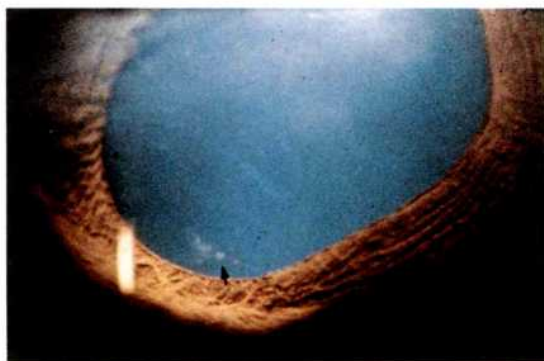


Fig. 1 First frame following 2.4 mJ application to capsule.

velocity occurring over the subsequent 20 milliseconds.

Particulate scatter was more easily observed after laser application to the iris. An intense white light was sometimes seen at the target centre in the frame coinciding with new observable events following each YAG pulse (first frame) (Fig. 3). This white light was distinct in contrast, tone, and position from the rapidly advancing wavefront of particles and was not observable in the next frame less than 1/400 second later (Fig. 4). However, other features related to the acoustic transient could be traced in subsequent frames as the wavefront progressed. Serial observa-

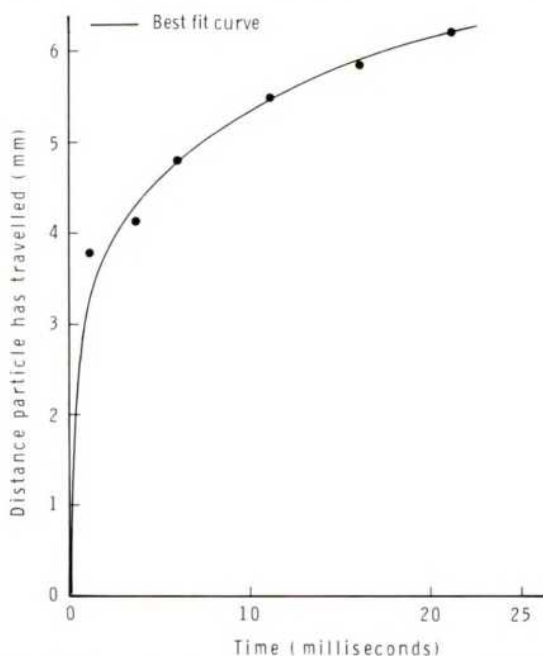


Fig. 2 Distance of bubbles from target plotted against time for single shot on capsule.



Fig. 3 First frame following 2.9 mJ application to iris. Note white light and cloud of particles above.

tions of all applications showed that this white light was present in 43% of first frames.

Measurements of the wavefront from a single application of 2.9 mJ to the iris showed a similar deceleration in particle velocity during the first 20 milliseconds following plasma formation (Fig. 5). A maximum time for initial particle displacement was again 1/400 s, resulting in a minimum mean initial velocity of 0.93 m/s (3.4 km/h). The particle displacement of 11.62 mm occurring at 100 milliseconds following laser application was the maximum observed before convection currents altered the linear dispersion of the particles (Fig. 6).

Particle scatter after the application of a train of pulses of 2.9 mJ each of which was separated by 20 milliseconds showed similar initial velocities and rate of decline (Fig. 7). However, succeeding pulses briefly increased the declining particle velocity and projected initial particles further from the target point while creating a new cloud of particles (Fig. 8).

Rapid tissue displacement was also observed by noting the acute anterior displacement of the iris



Fig. 4 Second frame, single iris shot, 1/400 second after Fig. 3.

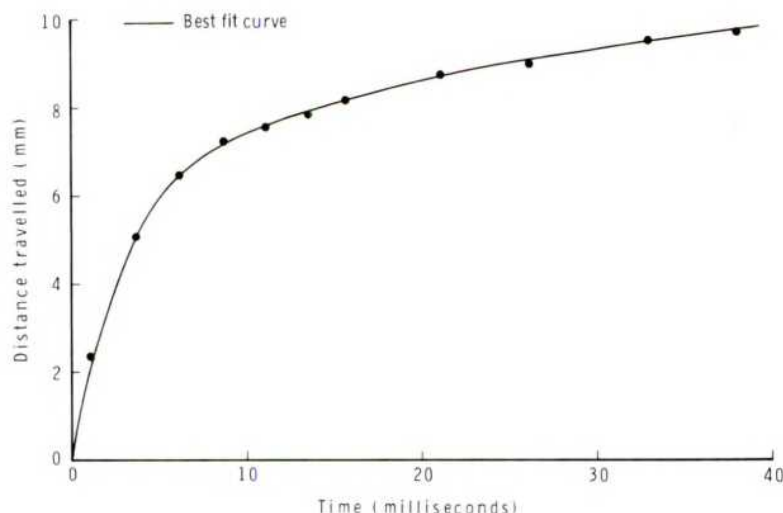


Fig. 5 Distance travelled by particles per unit time for single shot on iris.

(Figs. 3 and 8) with a peak to trough distance of 1.44 mm measured in the 'first frame'.

The cumulative effect of a train of five pulses in terms of the quantity of particles was observed on viewing the frame coinciding with the fifth pulse, 100 milliseconds following the first pulse (Fig. 9).

The film speed of 400 frames per second was verified, as pulses at 20-millisecond intervals were separated by eight frames on analysis.

Discussion

The cutting effect produced by the Nd/YAG laser results from events during and immediately following plasma formation. A rapidly expanding plasma volume at high temperature (approx. 10 000°C) produces an acoustic transient which generates a shock wave mechanically disrupting tissues round the target

centre.² These processes are necessary to produce the desired 'cutting' action but are accompanied by certain effects which may be undesirable. These include the ultraviolet light emitted by the plasma, acoustic shock waves, electromagnetic field stress, thermal conduction, the residual YAG energy past the point of optical breakdown, free tissue debris which may occlude drainage channels, and high velocity particle scattering.

Initial reports of complications subsequent to the clinical use of Nd/YAG lasers concentrated on the incidence of raised intraocular pressures, usually of a transient nature, and even suggested that there was no significant risk to the endothelium.^{3,4} Emphasis in animal models has been placed on endothelial damage from the direct mechanical effect of the Nd/YAG shock waves,⁵ and it has been suggested that peripheral iridotomies performed at a distance of >1 mm from the endothelium would be expected to produce no acute corneal endothelial damage.⁶

Vitreous collapse with anterior vitreous liquefaction and posterior vitreous detachment has been associated with retinal breaks and subsequent detachments following YAG laser capsulotomy.⁷

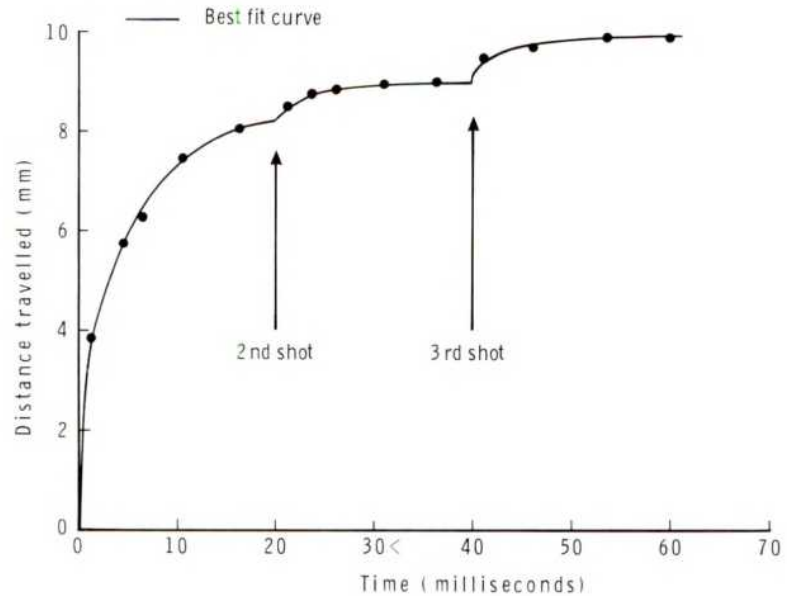
Until recently little mention had been made of the potentially damaging effects of high velocity particle scattering. Kerr-Muir and Sherrard suggest that the endothelial changes observed following Nd/YAG laser iridotomies and capsulotomies are likely to be due to particle bombardment of the endothelium, as endothelial damage occurred in quadrants remote from the target point.⁸ Their patients received treatments consisting of 1–20 bursts of up to 3–4 pulses per burst using energies up to 12.5 mJ per pulse—that is, well above threshold levels.

Our study shows that, even with threshold energy,



Fig. 6 Particulate dispersion 100 milliseconds following single 2.9 mJ laser application to iris.

Fig. 7 Distance travelled by particles plotted against time for train burst on iris.



high velocity particles are produced which may travel over 8 mm in the first 20 milliseconds after the application of a single pulse. Compared with single pulses, train pulses clearly create more particles, which are projected further from the target point so quickly as to be hardly discernible to the naked eye.

Even with a film speed of 400 frames per second the exact timing of a 12-nanosecond pulse cannot be determined, and therefore the mean initial velocities above are likely to be an underestimate. We believe the white light observed in the 'first frames' to be the spark emitted as free electrons and ions recombine following plasma formation as in a lightning bolt or static electricity discharge.²

As the plasma is estimated to emit light for twice the pulse duration (that is, 24 nanoseconds),⁹ any observation of a spark in a single film frame implies that plasma formation occurred during that 1/1200 second. The camera shutter is open for 1/3 of the total filming time and therefore on average 33% of YAG pulses would be expected to coincide with the interval when the shutter is open. An observed incidence of the white light in 43% of first frames would be in line with this order of probability.

If plasma formation can be accepted as occurring within the 1/1200 second recorded by a single frame, the minimum mean initial velocity of particles from the single iris pulse is 2.78 m/s (10.0 km/h). This

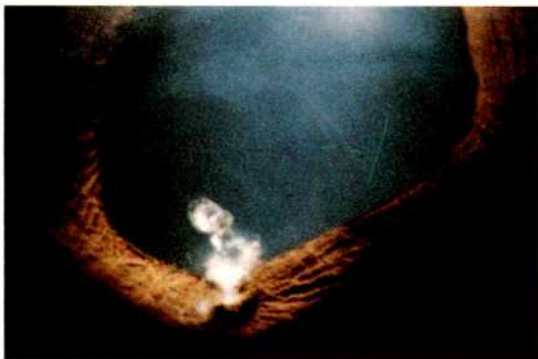


Fig. 8 Frame coinciding with second pulse during train burst on iris. Note white light above iris furrow with dense new cloud of particles at pupil margin.



Fig. 9 Frame coinciding with fifth pulse in train burst on iris, 100 milliseconds following first pulse.

figure assumes the pulse to be delivered immediately on the opening of the camera shutter.

Measurements of wave front distances in first frames including the white light phenomenon do not differ significantly from that recorded from the single iris pulse. Therefore, if the YAG pulse can be presumed to be delivered at the midpoint of the frame, the mean particle velocity in the first millisecond following plasma formation is 5.56 m/s (20.0 km/h).

In performing peripheral iridectomies the site chosen usually has an iris to cornea distance of <2 mm. A single threshold pulse will produce particles which may impact with the endothelium within a millisecond of plasma formation. These particles may be travelling at speeds in excess of 20 km/h and clearly would be expected to produce observable effects on specular microscopy.

New applications for the Nd/YAG laser are being reported with as many as 300–500 bursts being advocated for certain procedures.⁸ The potential harm from tissue distortion as well as endothelial and trabecular meshwork damage from high velocity particles should be considered when investigating clinical applications for the Nd/YAG laser, particularly on compromised eyes.

This study was supported by a grant from the Oxford District Research Committee

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Accepted for publication 18 September 1985.

Radiation chorioretinopathy

ANWAR ELMASSRI

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SUMMARY Three cases of postradiation retinopathy are reported. The findings are analysed. The exudates described by many authors are really infarcts of the choroid lobules. Chorioretinopathy is proposed as a better descriptive term, and three types are suggested. Diagnosis of the condition is important to spare unnecessary enucleation, as the infarcted areas may resemble a recurrence. Predisposing factors are discussed.

Radiation retinopathy might occur as a reaction to irradiation after cobalt-60 local application to a retinoblastoma. The condition usually occurs several months or years after the presumed complete cure of the tumour, and it produces a more or less marked disturbance of vision which causes great alarm to both the patient and the doctor. The following cases demonstrate the series of events caused by such a complication.

Case reports

CASE 1

A female infant aged 1½ months presented on 18 May 1982 with a central raised mass with ill-defined and irregular margins involving the macular region of the left fundus. The right eye was enucleated because of retinoblastoma in an advanced stage, which proved on pathological examination to be well differentiated. A C-shaped cobalt-60 10 mm diameter applicator was applied over the macular area and embracing the optic nerve on its temporal margin, giving a dose of 19 000 rad over the base of the mass and 4000 rad over its apex. Seven days later the applicator was removed and the mass showed a good response in the form of few haemorrhages on the surface together with some diminution of the size and with well defined margins. A week after that the mass became much smaller and completely avascular, an indication of a good reaction to the local radiation therapy. The patient was followed up every month, with no change in either the size or pattern of the remaining mass.

On 30 November 1983 the mass started to show changes in the form of minute haemorrhages on the

surface and around its margins; deep, white patches had appeared around the mass and throughout the fundus, together with intervening telangiectases. The white patches were well defined, avascular, and deep to the retinal vessels. They were separate and appeared as a mosaic, but some coalesced to form relatively large triangular areas with the apex towards the optic disc. At the periphery some patches were large and pearly in appearance and were suspected of being recurrences. One month later the lesions were more severe, with an increase in the haemorrhages and telangiectatic vessels, while the mass remained small in size but covered with haemorrhages.

A course of external beam irradiation was started one week later, as the condition was wrongly diagnosed as a recurrence. After 12 sittings of this treatment, when the eye had received another 4000 rad, the fundus showed severe telangiectasis and diffuse haemorrhages, some of them preretinal, throughout the central and peripheral regions. Some of the preretinal haemorrhages were observed to increase in size when the eye was slightly pressed during movement to facilitate examination of the periphery.

Three months later the massive haemorrhages were completely absorbed, but few small haemorrhages and telangiectatic vessels remained. Recurrences in the form of small or large haemorrhages occurred every now and then, probably owing to pressure on the eye by the patient affecting thin walled telangiectatic vessels. The deep white patches remained, though they were small and had a slightly pigmented dimpled centre. The optic nerve showed atrophy, and the patient's vision deteriorated to hand movements. The patient is still under observation and has shown no subsequent changes.

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CASE 2

A male infant 7 months old presented with a large mass in the left macula. The right eye was normal. On 10 November 1982 a C-shaped cobalt-60 applicator 15 mm in diameter was applied over the macula and embracing the optic disc. Seven days later the applicator was removed and the mass showed marked improvement. It became smaller and showed well defined margins and a nodular surface indicating areas of calcification.

Routine follow-up was carried out weekly, bi-weekly, and monthly, with the mass showing continual reduction in size and increase in calcium deposition. From the start the patient was given a course of chemotherapy.

Six months later and while the patient was still under chemotherapy the nasal side of the mass started to show a few haemorrhages, and a recurrence was suspected. Two weeks later a course of external beam irradiation of 1500 rad was started on the assumption that the previous local irradiation had been insufficient for such a relatively large mass. One month later haemorrhages on the surface of the mass and throughout the fundus were seen, together with deep polygonal white patches of different sizes giving in some areas a mosaic appearance, choroidal in nature, and deep to the retinal vessels. Haemorrhages and telangiectatic superficial retinal vessels were present throughout the fundus. At the end of the irradiation course most of the telangiectatic vessels had disappeared, but many deep white patches remained.

Three months later haemorrhages started to appear again over and in the retina surrounding the mass but not at the periphery of the fundus. These absorbed after a short time, to reappear every now and then. As the patient was under chemotherapy a cytomegalovirus retinopathy was suspected, but cultures from saliva and urine were negative. When the condition was discovered, the chemotherapy was not stopped, as a recurrence was suspected.

CASE 3

A 40-day-old male baby presented on 4 December 1979 with an advanced retinoblastoma in the left eye which necessitated enucleation. Examination of the right fundus revealed a crescentic mass embracing the upper and temporal area of the optic disc margin. Photocoagulation was done, but, as the mass was considered to be incompletely affected, a C-shaped, 7 mm diameter applicator was inserted above and temporal to the optic nerve. The mass responded satisfactorily, and the patient was considered to be completely cured. A monthly routine follow-up was carried out.

On 27 January 1981, that is about one year after

insertion of the cobalt-60 plaque, a black circular pigmented patch about 1.5 disc diameters was seen outside the macular area. The patch was flat, polygonal, and had a slightly raised irregular white mass at its upper and medial margin. Its centre was dimpled and faintly pigmented (Fig. 1). A recurrence was suspected, and a routine examination at short intervals was resumed. Six months later a few telangiectatic vessels were discovered above and temporal to the peripapillary mass.

The clinical picture remained unchanged for about two years, but on 12 April 1983, that is just over three years after application of the disc, an unusual picture was seen. Several white patches of regular polygonal margins close to each other and in mosaic formation covered the area above the macula and reached the previously detected lesion (Fig. 2). The new patches were not pigmented, were of various sizes, and were shallow at the centre. A few coalesced, and some were large, measuring about 2 disc diameters. They were all deep to the retinal vasculature. After a time certain changes occurred. The first patch to be discovered became white, with only a trace of pigment at its shallow centre. The other patches have remained unchanged up to the present.

Discussion

Radiation retinopathy is not often noted as a complication of radiotherapy for malignant melanoma or



Fig. 1 A late stage of the early choroidal infarct (arrow) together with the newly developed infarcts.

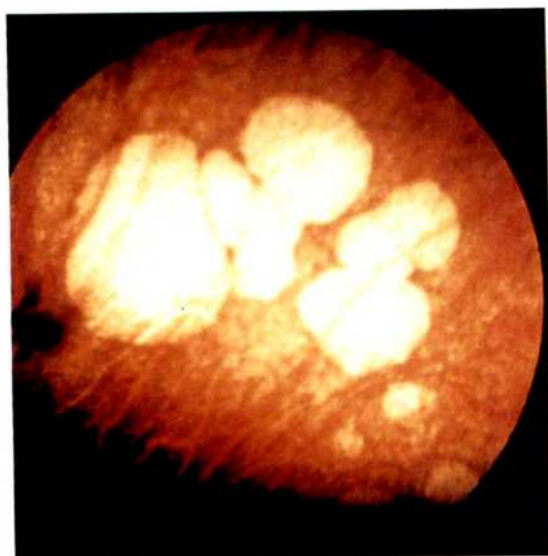


Fig. 2 Choroidal infarcts forming a mosaic with regular polygonal margins bridging the region above the macula.

retinoblastoma. Reese¹ refers only to postradiation vascular changes, while Ellsworth² relates the condition to vascular necrosis produced by damage to the endothelium of the retinal vasculature.

Stallard^{3,4} states that complications due to radiation therapy by application of cobalt-60 discs in the treatment of retinoblastoma occur when a large dose is applied, and especially if there is more than one mass or if the tumour is large or embraces the large branches of the central retinal artery. At the same time he refers to the role of the early vascular damage in destruction of the tumour mass. This vascular damage includes both a narrowing of the small vessels and rupture of the capillaries. He reported 15 cases of late complications of radiation. The delay before their appearance ranged from 9 to 18 months and even 4-5 years in one case. The resulting haemorrhage may be very small or large enough to necessitate enucleation. In four of his cases perivascular exudates occurred—after 11 months in two cases and after three years in a third, and with circinate form in the fourth. The exudates were chiefly present in the inner nuclear layer. He related the macular changes to choroidal vascular involvement.

MacFaul and Bedford⁵ reported on the delayed effect of radiation treatment of intraocular tumours. They stated that radiation retinopathy rarely occurs after irradiation of the whole eye and that retinal and choroidal changes are seen commonly after local irradiation of retinoblastoma or malignant melanoma and are usually apparent some months after the completion of the treatment. The vascular

changes were narrowing and obliteration of the retinal arteries, veins, and capillaries, with perivascular sheathing if massive radiation had been carried out, especially if the plaque was applied a few millimetres from the optic disc. Haemorrhages and exudates appeared early and sometimes late in and around the treated area after focal irradiation of a juxtapapillary retinoblastoma. Exudates are generally hard and white, presumably owing to phagocytosis of the tumour debris or haemorrhage together with infarction of choroid and retinal tissue close to the tumour.

In a study of the fundus by fluorescence angiography in three cases of malignant melanoma treated with cobalt plaque in which postradiation retinopathy occurred Hayreh⁶ concluded that the retinopathy takes various forms: a focal obliteration of the capillaries due to endothelial damage, microaneurysms or telangiectasia or both, and neovascularisation. Cotton wool spots sometimes present were thought to be due to focal occlusion of small retinal arterioles producing retinal infarcts. A circular cobalt plaque was applied in his first case, a C-shaped plaque in the second, and possibly a circular one in the third.

Blodi and Watzke⁷ stated that the effect of radiation on the retina and retinal tumours consists of vascular changes mainly in the form of thinning of the vessel wall leading to haemorrhages and in modification of the neoplastic cells.

Char *et al.*⁸ noted that, in five out of seven cases of posterior pole melanoma, radiation retinopathy developed after treatment, with resultant decrease in vision. They stated that this type of retinopathy is a form of occlusive vascular disease with a predilection for capillaries, causing obliteration of the lumen, formation of microaneurysms, telangiectasis, neovascularisation, cotton wool spots, circinate macular exudates, perivasculitis, and haemorrhages. They also stated that radiation retinopathy with a resultant decrease in vision is probably much more common than has been reported, since its onset is usually two to three years after therapy and may be as long as 15 years. Because of this complication they ceased using cobalt plaque in the management of posterior pole melanomas.

C-shaped cobalt plaques were used in the reported cases as a treatment for posterior peripapillary or macular retinoblastoma. This treatment was considered to be more suitable than external beam irradiation with its possible complications to the lens or the surrounding skin of the orbit. It has now been discontinued, as the three reported cases showed a typical postradiation retinopathy described by the above mentioned authors.

My interpretation of the accompanying so called

exudates is different. These exudates are actually choroidal infarcts of different sizes according to the size of the affected choroidal terminal arteriole. The choroidal lobules, so called by Hayreh,⁹ with their central terminal arterioles act as separate physiological units and become infarcted if the supplying vessel is occluded. Infarcted lobules become white and have a polygonal outline; together with neighbouring infarcted lobules they form a mosaic having the same appearance as is seen during fluorescein angiography of the normal choroid.

Choroidal infarcts, like cerebral infarcts, are usually initially white, because there is hardly any anastomosis and the vessels occluded are so small that obliteration is usually complete from the start. Actually the grey and yellow exudates described by Blodi & Watzke⁷ are choroidal infarcts, as their figs. 2, 3, and 4 show.

If a large choroidal vessel is involved, all the lobules supplied by this vessel become infarcted, producing the diffusely oedematous triangular areas with the apex towards the central region described by Amalric.¹⁰

Because of oedema due to rapid onset of the infarction the margins of the lobules coalesce, and the area looks as if it is one large patch. When the oedema subsides, the area resumes its mosaic form.

The condition can be considered as a choroidopathy due to a late toxic effect of radiation treatment. It is usually accompanied by the characteristic retinopathy, as in cases 1 and 2, but sometimes it occurs alone or with only very little retinopathy as in case 3. The condition should be termed radiation chorioretinopathy, as the choroid is nearly always constantly involved.

Postirradiation toxicity may be divided into two types:

Type 1. Early radiation toxicity. This is common and occurs in nearly every case. It is a good sign, as it denotes the necrosis of the tumour with rupture of its capillary contents.

Type 2. Late radiation toxicity. This may be (a) mainly retinopathic, which is uncommon; (b) mainly choroidopathic, which is rare; or (c) chorioretinopathic, which is the commonest.

The late type may occur months or even years after the irradiation. Sometimes it comes in episodes; each

is probably predisposed to by small unnoticed traumata such as rubbing the eye, which cause bleeding from the extremely friable telangiectatic small vessels and capillaries.

It seems that the application of a cobalt plaque, especially the C-shaped type, over masses in the macula or near the disc causes direct pressure on the main ciliary and retinal vessels which are present in this area. This is why it is agreed that tumours in this region should be treated by other means if possible such as photocoagulation or external beam irradiation. However, the retinopathy occurred in one unreported case which had the plaque applied at the equator and in another case in which external beam irradiation was the only treatment. It thus seems that factors other than overdosage or proximity to the macula or the optic disc may play a part in producing the condition. As the retina is a part of the nervous system, one should not be surprised by the similarity of the late radiation effect to that which occurs in the brain or the spinal cord after radiation, either directly or to neighbouring structures.¹¹

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Pattern electroretinograms become abnormal when background diabetic retinopathy deteriorates to a preproliferative stage: possible use as a screening test

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SUMMARY The pattern electroretinogram (PERG) and other tests were given to a selected group of patients with diabetes, ranging from those who had no retinopathy or fundusoscopic changes to those in the preproliferative state. None had visual symptoms. The PERG was found to be normal in patients with microaneurysms and a few blot haemorrhages. However, when cotton-wool spots and angiographic evidence of areas of capillary non-perfusion were present, the PERG was reduced below the normal value. Similar changes occurred with the oscillatory potentials of the ERG evoked by an intense flash, but the results were more variable. So in the individual patient the test is not a reliable indicator of the progress of the retinopathy. The value of the PERG in screening is discussed.

While the electroretinogram (ERG) evoked by diffuse flashes of light remains normal in cases of diabetic retinopathy unless gross retinal damage or vitreous haemorrhage has supervened,^{1,2} minor components of the electroretinogram, the oscillatory potentials (OPs) have been reported to be affected earlier^{3,4} and to be an indicator of the progression of the condition.⁵ The small pattern electroretinogram (PERG) evoked by reversing a black and white pattern may be produced in a different manner from the normal ERG^{6,7} and has been found to be reduced by retinal diseases which do not affect the ERG itself.⁸⁻¹¹ In a preliminary study of the PERG in the eyes of patients who were about to have argon laser panretinal photocoagulation for advanced diabetic retinopathy (Arden, unpublished) it was found that the PERG was uniformly abnormal. We have therefore recorded PERGs from the eyes of diabetics with varying degrees of milder retinopathy, and now report that, while mild background retinopathy does not affect the PERG in every case of a small series, the response is abnormal in the presence of fundu-

scopic and angiographic evidence of capillary non-perfusion despite the absence of visual symptoms.

Patients and methods

Patients were drawn from the diabetic clinics of the Middlesex Hospital and the Whittington Hospital, either by consultation of computer records or by searching the notes. The criteria for entry into the trial were (a) no cardiovascular, neurological, or other ocular disease should be known to be present, and there should be no eye symptoms; (b) the corrected visual acuity should be better than 6/12; (c) the age of onset of diabetes should be no greater than 50; and (d) no result would be included if the eye had diabetic retinopathy which required immediate laser treatment.

The reason for these requirements was to eliminate patients with unrelated conditions which themselves might affect the PERG. The most common of these are uncorrected refractive error, glaucoma, amblyopia, cataract, optic neuritis, degenerative maculopathies, and hypertensive eye disease—and proliferative diabetic retinopathy itself. As a result of the selection almost all the patients had diabetes of

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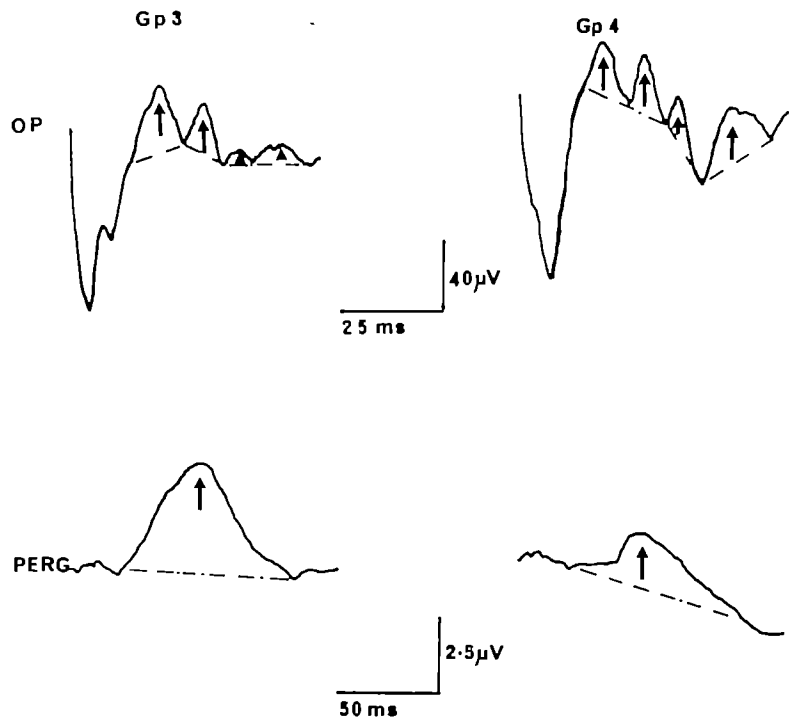
juvenile onset and required insulin injections, though a number of them developed the condition in early adult life. We attempted to select patients with all grades of retinopathy, including those with normal fundi.

The patients selected were interviewed by the staff of the diabetic clinics, and the nature of the proposed investigation and what was involved for each patient was explained. Informed consent obtained, the patient was then referred to the Electrodiagnostic Clinic, Moorfields Eye Hospital, where electrophysiological investigations were performed. The PERG was usually recorded from one eye, without pupillary dilatation, under the standard conditions described in the caption to Fig. 1 and in previous papers. When there was an interocular difference, the eye with the better acuity was tested. Oscillatory potentials were obtained on the fellow eye after pupillary dilatation as described by Bresnack *et al.*,³ and the records were measured in the way those authors specify. In one case the fellow eye had proliferative retinopathy, so the result was not included. In one patient the PERG was obtained

without the patient's wearing spectacles to correct myopia, and this result was discarded. In some cases both tests were done on each eye and the two results averaged. The recording system consisted of a specially built amplifier, under the control of a PDP11/23 computer programmed to average and display the results. The system was driven by interrupts from the TV pattern generator. Ophthalmological investigations were performed and the degree of disease classified without reference to the electrodiagnostic findings, and, since a number of patients were thought to have no retinopathy, the investigation was essentially 'double blind'. Colour photographs of the fundus were obtained on all patients, and the region photographed (in those patients with fundus abnormalities) were specified after funduscopy. Only in those patients with ophthalmologically normal fundi or those in whom only a few microaneurysms were visible was fluorescein angiography omitted.

On the basis of the photographs the patients were divided into four groups: I normal fundus; II few microaneurysms only; III microaneurysms, a few

Fig 1 Pattern ERGs (PERGs) and oscillatory potentials (OPs) from the eyes of a subject with grade III retinopathy (see Fig 2) and (right) grade IV disease (see Fig 2). PERGs are the computer calculated average of three records, each derived from 150–200 repetitions of the stimulus. Artefact rejection was incorporated. The response was recorded with a gold foil electrode on the cornea, an indifferent electrode of the ipsilateral temple near the lateral canthus, and a forehead earth electrode. The stimulus consisted of 30' squares displayed on a TV monitor which subtended $15 \times 22^\circ$ at 1 m, and had a mean luminance of 100 cd/m^2 . The pattern reversed eight times per second. The contrast was nearly 100%. The white surround to the monitor was illuminated to 200 cd/m^2 . The OPs were obtained by light from a 40 J photographic flash tube, cycle time 20 s, delivered to the eye through a rigid Perspex light pipe 2.5 cm diameter, the end of which was placed less than 1 cm from the cornea. Electrodes were as



for the PERG. The eye was preadapted for two or more flashes, and then the responses to the succeeding four flashes were averaged. This sequence was repeated three times. The dashed lines drawn show the method of measurement: two troughs were joined and the peak height estimated at the times indicated by arrows from the baseline thus formed. The voltages shown in Table 1 are the sum of the first five oscillations (following Bresnack *et al.*³) for the OPs. A similar procedure was followed for the PERGs, but there was only one peak to measure. The responses are chosen to be average amplitude for groups III and IV.

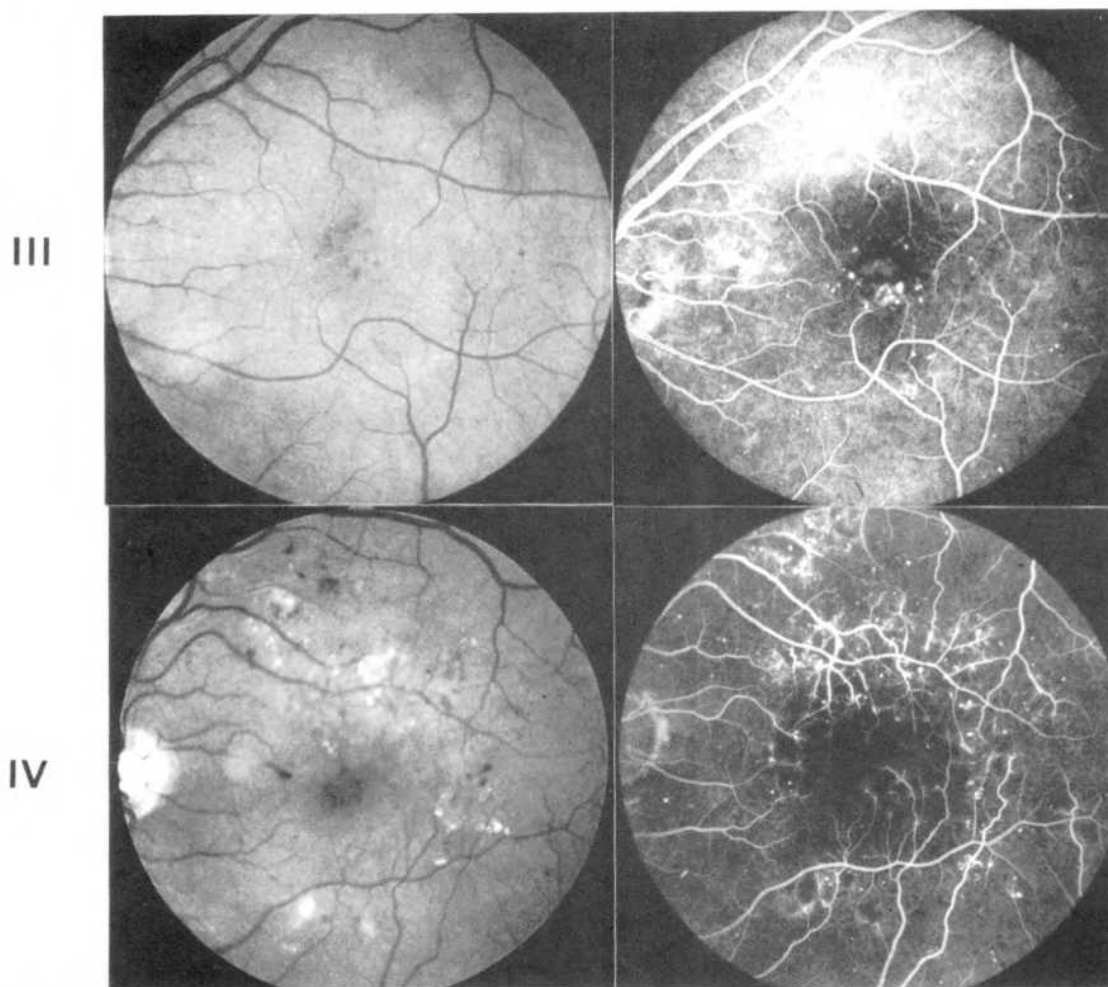


Fig. 2 Fundus photographs and angiograms of a representative patient from groups III and IV. The patient from group III had a PERG of $4.2 \mu\text{V}$. The patient whose fundus illustrates group IV produced the largest PERGs of the group— $2.3 \mu\text{V}$. Note that not only are there more microaneurysms and cotton-wool spots in his fundus, but also there are darker areas on the angiogram which indicate regions where capillary non-perfusion is occurring: such areas are absent in the angiograms of group III.

small 'blot' haemorrhages, and/or hard exudates, but not further changes; no evidence of capillary non-perfusion on angiography; IV the above, plus cotton-wool spots, pronounced leakage, and evidence of capillary non-perfusion on angiography.

In the absence of angiography it is possible that patients classified as group I might include some from group II. No patient in group IV had proliferative retinopathy. There were no new vessels at the disc or peripherally. The aim in classification was to separate patients who had background retinopathy of a level not requiring surgical intervention (group III) from those in whom surgical intervention might be required

in the near future. Characteristic changes are shown in Fig. 2.

Results

Table 1 summarises the results. The mean PERG value for group I was larger than was previously found for a group of normal persons¹³ but not significantly so, and this was probably associated with the fact that the patients in this group were younger and had very good eyesight. The OPs were in the range reported by previous workers.⁵ The remaining groups were similar in their ages and duration of

Table 1 Comparison of findings in four subgroups of diabetics

Group*	I	II	III	IV
Number of patients	8	13	17	15
Sex	4 M	6 M	10 M	9 M
Age (mean, SD, and range) yr	32.6±5.3 (27–39)	42.3±14.6 (25–71)	42.0±12.8 (25–63)	43.3±12.2 (21–61)
Duration of diabetes yr	15±6	24±14	18±8	19.6±9
Number with onset age >20† yr	0	2	7	7
Visual acuity: range and indication of distribution‡	6/4–6/5 2 at 6/4 6 at 6/5	6/4–6/9 1 at 6/4 2 at 6/5 8 at 6/6 2 at 6/9	6/5–6/9 6 at 6/5 8 at 6/6 3 at 6/9	6/5–6/18 4 at 6/6 9 at 6/9
Number not on Insulin	0	2	2	3
PERG (mean, SD, and range) µV	4.8±.9 (3.7–6.2)	3.6±.9 (2.6–5.4)	3.5±.7 (2.4–4.8)	1.8±.38 (1.2–2.5)
Oscillatory potential (mean, SD, and range)‡ µV	90±17 (126–70)	74±20 (127–56)	67±13 (89–44)	54±17 (83–20)

*See text for definition.

†Data not available for one patient in groups I and II, three in group III, two in group IV.

‡Data not available for one in group III, three in group IV.

§If not shown, extreme values for visual acuity obtained in one patient only.

disease. In groups II and III the mean PERG value was nearly exactly that found previously for normal subjects. There was a slight progressive decrease in the OPs, so that the mean OP in group III was less than the lower limit of normal given by Bresnick *et al.*⁵ Group IV, with more advanced disease, did not differ from the groups II and III in terms of age or duration or type of disease, but the visual acuity was on the whole slightly reduced. In only one case was the reduction great enough to be counted as outside the normal limit. In this patient perimacular retinal changes were evident, but there was no obvious macular oedema. There was a very striking and highly significant reduction in the mean PERG voltage. The probability of the patients in groups III and IV coming from the same population was less than 0.02 by Student's *t* test. The mean value in group IV was half that in group III, and significantly below the value (2 standard deviations below the mean) accepted in the clinic as the lower bound of normal (2.4 µV for persons under 50 years of age). In one case in this group, a patient aged 30, the value was the average of that for both eyes, individually 2.2 and 2.7 µV. In two more cases the value was 2.3 µV (ages 38 and 49). In all other cases the value was <2 µV.

The oscillatory potentials appeared to behave in a slightly different manner. There was a reduction in the mean values for each successive group, which was not so exaggerated for group IV. The scatter of results was larger, and therefore the mean result, and the result in any individual, was not significant. The mean age of patients in group IV was rather larger than for the other groups, but the duration of diabetes was not greater.

Discussion

While sensitive tests of retinal function such as contrast sensitivity may show abnormalities due to diabetic retinopathy,¹⁵ they tend to have a high incidence of false positive results, unless the criteria for abnormality are set so that there is an unacceptable level of false negative results, or the test is made so detailed and prolonged that it is clinically inapplicable. For this reason the report that OPs are abnormal in the deteriorating diabetic retina was of considerable interest because the test is quick to administer.

The results on the OPs are the first we have obtained with this technique. We have no normal population with which we can compare our results. The patients without retinopathy have OPs of the size previously reported.⁵ If we use the lower limit of normal determined elsewhere, then none of group I are abnormal, 7 of group II, 10 of group III, and 11 of group IV are abnormal. There is no significant distinction between the group averages or the proportions of individuals abnormal between groups. The average OPs deteriorate, as previously reported, but do so in the presence of mild background retinopathy. Thus the result is not very useful in the individual.

The present results suggest that the PERG provides more reliable data than the OPs. However, we have recorded PERGs in our clinic for some years, and the test is done very frequently. Apart from the small scatter in the results the reduction in the PERG appears to come about at the particular phase of the disease when referral to an ophthalmologist becomes necessary.

In several retinal conditions the PERG is grossly reduced even when the disease is mild.^{13,14} In cases of inherited juvenile maculopathy, disease of a severity which causes any reduction in visual acuity has a gross effect on the PERG. However, the relationship cannot be simple, because refractive errors which cause reduction in visual acuity produce a much smaller effect on the PERG. The patients in this series did not suffer specifically from diabetic maculopathy, and loss of visual acuity even in group IV was minimal. However, in this group there are very severe reductions in the PERG, which strongly suggests that the abnormality in the PERG appears when the capillary circulation is affected, and not earlier. In view of the fact that the PERG tests the function of the central retina, the gross reduction occurring in all cases in group IV at first seems surprising, since the areas of non-perfusion may occur in the peripheral retina. However in a separate study¹⁵ of preproliferative retinopathy with peripheral non-perfusion it has been found that Amsler chart testing shows transient metamorphosis, and fluorescein angiography shows evidence of microvascular abnormalities in the posterior pole. It would seem therefore that there are often minor changes at the posterior pole in patients whose main pathology consists of peripheral capillary closure, and this may be causing the change in the PERG.

Although the series is small, there is little overlap between groups III and IV. Even on the basis of one test all the patients of group IV could be distinguished from those of III, if we allow the worse eye of the patient for whom we have results in both eyes. Even if the patients are judged on the severest criteria, which make no allowance for age variation, only three of group IV could be considered normal, and no one in the other groups would be abnormal. If the PERG was introduced for screening diabetics, serial tests would be done on each patient, and it should thus be possible to spot deterioration in any individual, even if the decrease was not so gross as appears in Table 1. Some of the individuals in group IV may have benefitted from immediate surgical intervention, but in no case was it mandatory, and therefore it is likely that, in some cases at least, serial testing might show a repeated PERG abnormality before the patient was in danger of losing vision. Advanced warning of deterioration would therefore be possible, as shown in the follow up findings with the OPs.¹

The method of patient selection may have biased the results, so it is not wise to speculate about the applicability of the test to patients in general. There are two important differences between the patients tested and the general population. Firstly, we have excluded anything except the mildest form of diabetic

maculopathy by the entry criteria, which demanded a normal visual acuity. However, in other maculopathies the PERG has been found to decrease early in the disease,¹³ and there is no reason to suppose that this will not be the case in diabetes. Secondly, although in this series we attempted to exclude anyone with any pre-existing eye condition, diabetes is found mainly in older people, in whom eye disease is prevalent. The progressive development of a cataract should cause a reduction in the PERG unrelated to a retinopathy, because the effective contrast in the stimulus is reduced by a cataract (Hamilton AM, Urey H, in preparation). If the patient did not have an adequate spectacle correction, this too would affect the PERG. Thus interpretation of test results in the unselected individual patient may require additional clinical examination.

However, the PERG has certain advantages as a screening test. The patient's pupils do not need to be dilated, so there are no sequelae to the test, as there are with OP testing or funduscopy, which require mydriasis. In co-operative patients the actual recording time need be no greater than a minute or two; introducing the patient to the test, and attaching the electrodes takes longer than the test itself. Specialised equipment is required, but it is a fraction of the cost of that needed for fundus photography.

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Fibroblast radiosensitivity and intraocular fibrovascular proliferation following radiotherapy for bilateral retinoblastoma

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SUMMARY A 5-day-old female patient was found to have large hereditary retinoblastomas in the posterior pole of each eye. The patient received radiation treatment over a 39-day period, with each retina receiving 4600 rad. Two weeks after the complete treatment the tumours had regressed to approximately one-quarter of their original size. By 14 weeks following completion of radiotherapy the patient had developed in each eye extensive iris neovascularisation with progressive closure of the filtration angles, secondary glaucoma, and retinal detachments resulting from fibrovascular proliferation on the retinal surface. Radiosensitivity studies were from separate conjunctival biopsies obtained before and after radiation. These showed a D_0 (calculated survival curve parameters, defined in the Methods section) in the exponential growth phase of 110 prior to radiation and a postirradiation exponential growth phase D_0 of 70. Karyotype studies showed several chromosomal abnormalities following radiotherapy. The clinical course and pathology findings are thought to represent an unusually severe orbital and ocular response to radiation therapy. These findings are consistent with our hypothesis that some patients with hereditary retinoblastoma may have a defect in the accumulation repair of x-irradiation induced DNA damage.

Recent studies have shown that fibroblast cultures from patients with hereditary retinoblastoma have an increased mean radiosensitivity when compared with fibroblasts obtained from normal controls or fibroblasts from the non-hereditary group.^{1,2} This observation has been of particular interest because patients with hereditary retinoblastoma, as generally determined by bilateral involvement or a known family history of the disease, subsequently develop second tumours at sites distant from the orbit as well as within the irradiated field following radiotherapy.³ We recently studied fibroblast sensitivity to x-irradiation in an infant with bilateral retinoblastoma before and after radiation therapy. Increased sensitivity to

x-irradiation and multiple chromosomal abnormalities in conjunctival fibroblast cultures were observed following treatment. Moreover, this patient had an unusually severe clinical response to radiotherapy, with a rapid onset of iris neovascularisation and preretinal fibrovascular proliferation which led to loss of both eyes despite regression of the intraocular tumours.

Case report

The patient, a girl, was found to have large retinoblastomas in the posterior pole of each eye at the age of 5 days. The patient's father had a history of bilateral retinoblastoma which had been treated by enucleation of one eye and radon seed implantation in the other. At the time of initial diagnosis there was

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no evidence of intraocular neovascularisation. Bone marrow aspiration and lumbar puncture showed no evidence of tumour cells.

Radiation therapy of both eyes was carried out for a total of 23 treatments over 39 days. A 4 MeV linear accelerator was used, with the patient under anaesthesia with ketamine hydrochloride. Both eyes were treated by anterior and lateral portals with a lens block used on the right eye for the full treatment and on the left eye for the last six days. Initially, 600 rad were given to the lateral fields without anterior supplement. Then the full four fields received the remainder to a total dose of 4600 rad. It was estimated that the right iris with the lens block received a minimum dose of 690 rad to a maximum dose of 2230 rad at the periphery. The retina in that eye received 4600 rad except for a small portion directly posterior to the lens. The left iris received a minimum of 1754 rad to a maximum of 2230 rad, and the retina again received 4600 rad.

Substantial tumour regression was noted soon after radiotherapy. Two weeks after the completion of the treatment course the tumours had regressed to one-quarter of their original size. The patient was examined under anaesthesia at monthly intervals. When examined at age 5 months—14 weeks following completion of radiotherapy—she was found to have extensive iris neovascularisation, partial closure of the filtration angle in each eye, and associated secondary glaucoma. Retinal detachments in each eye were found. No new tumour or recurrence of tumour growth occurred. Because of intractable neovascular glaucoma and pain no evidence of visual function in either eye, enucleation of the left and then the right eye was performed. The patient progressed satisfactorily after the operation without evidence of orbital or distant tumour. Striking shrinkage of the orbital space has occurred, associated with dry conjunctiva sockets. Her gross motor development has been slow.

Materials and methods

RADIOSENSITIVITY STUDIES

Small conjunctival biopsy specimens were obtained at the time of initial examination under anaesthesia and diagnosis (designated B-0821), and at the time of enucleation (following radiotherapy) (designated B-814). Fibroblast cultures were established by methods previously described.⁴

For survival experiments exponentially growing cells were detached with 0.25% trypsin in calcium-free and magnesium-free Earle's balanced salt solution and seeded at appropriate numbers into triplicate 10 cm diameter Falcon tissue culture dishes containing 10 ml of culture medium. Feeder layers

were not used, and the density of cells in these experiments never exceeded 4×10^4 /dish. Dishes were irradiated 18 hours later (multiplicity=1) at room temperature and ambient atmosphere with a 220 KVp General Electric Maximar unit operated at 15 ma and yielding a dose rate of 80 rad/minute as determined by a Victoreen ionisation chamber. The half-value layer of the beam was 0.5 mm of copper. At least four doses, ranging from 50 to 700 rad, were used per experiment. After irradiation the dishes were returned to the incubator, the medium was changed every five to seven days, and the colonies were fixed and stained after 12 to 21 days. Satellite colony formation was not observed under these conditions. Experiments were scored under a dissecting microscope with colonies composed of 50 or more

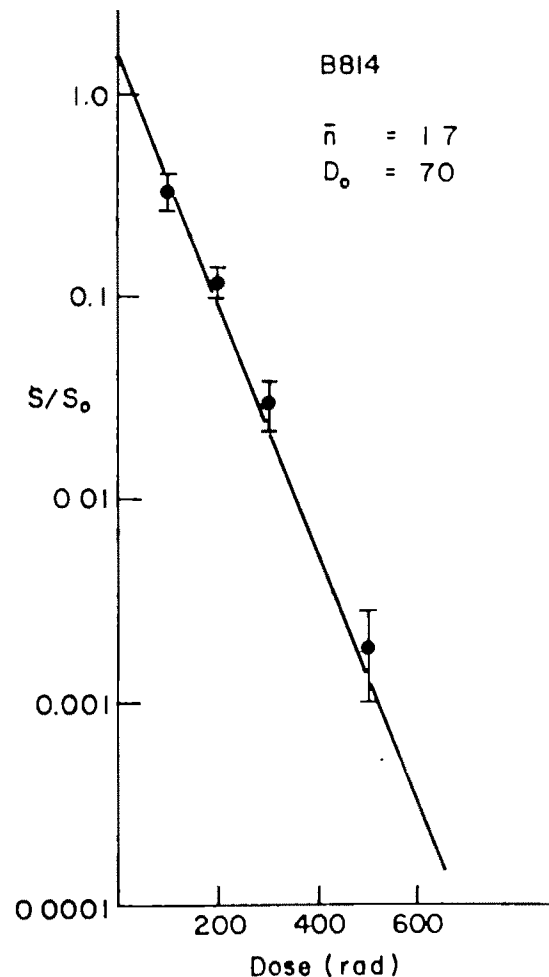


Fig 1 Graph shows x-ray survival curve parameters determined by least-squares regression analysis for cultured fibroblasts from preirradiation period. $D_0=110$, $n=1.6$.

cells considered as survivors. Cloning efficiencies ranged from 4.0 to 97.5%. The calculated survival curve parameters were the D_0 in rad (inverse of the slope of the straight-line portion of the survival curve) and n (a measure of the magnitude of the shoulder region of the survival curve). They were both derived from a least-squares regression analysis of points above 100 rad.

To eliminate the effects of differences in cell cycle distribution accounting for differences in radio-sensitivity in cultures derived from pre- and post-radiotherapy biopsies, x-ray survival experiments were performed on density-inhibited plateau phase cultures. Over 90% of cells in these cultures are in the G_1 phase of the cell cycle. Cultures were grown to confluence and the medium changed daily for three days. Irradiation was done on the fourth day. Cells were subcultured immediately after irradiation.

CHROMOSOME STUDIES

Logarithmically growing cultures of both the cell lines B-8021 (the preradiation cell line) and B-814 (the postirradiation cell line) were treated with demecolcine (Colcemid) at a final concentration of 0.1 $\mu\text{g/ml}$ and slides were stained with quinacrine mustard (50 $\mu\text{g/ml}$) as described previously.⁵ Well spread and well banded metaphases were photographed with a Leitz Ortholux microscope equipped with an Orthomat camera. The prints were made on Agfa paper.

PATHOLOGY

The eyes were obtained at the time of enucleation and immediately placed in glutaraldehyde-formalin fixative. They were embedded in paraffin, sectioned, and examined by haematoxylin and eosin and periodic acid Schiff stains in accordance with methods previously described.

Results

Figs. 1 and 2 show x-ray survival experiments from separate biopsies obtained before and after treatment with 4600 rad in 39 days. The D_0 of the preradiation biopsy of cells in the exponential growth phase was 110 ($n=1.6$); in the plateau phase D_0 was 111 ($n=22$) (immediate subculture; data not shown). The D_0 of the postirradiation biopsy in the exponential phase of growth is 70 ($n=1.8$) (Fig. 1) and the plateau culture phase $D_0=85$, after immediate subculture (data not shown).

HISTOPATHOLOGY

The histological appearance of both eyes was similar. The residual tumours were limited to several small foci with marked calcification and necrosis (Fig. 3a).

No cytologically viable tumour cells were seen. Marked iris neovascularisation with closure of the filtration angle was noted (Fig. 3b). Extensive pre-retinal fibrovascular membranes were present, with large traction retinal detachments observed. The retina itself showed extensive loss of ganglion cells, as well as marked cystic changes in the inner retinal layers (Fig. 3c). Occasional retinal vessels were seen to be narrowed and obliterated.

CHROMOSOME STUDIES

Fourteen metaphases were photographed and analysed, and four of these were karyotyped from a fibroblast culture obtained prior to radiotherapy (B-8021) (Fig. 4). All cells showed a diploid female karyotype. Five of the 14 metaphases showed random chromosome loss due to cell breakage. The fibroblast cell line obtained after radiation therapy (B-814) also had a modal number of 46 chromosomes (Fig. 5). In seven

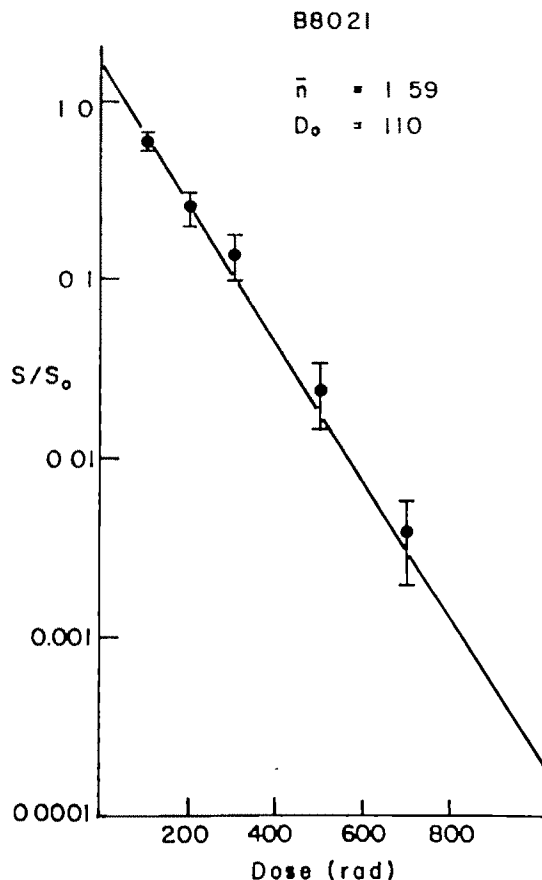


Fig. 2 Graph shows x-ray survival curve parameters determined by least-squares regression analysis following radiotherapy Postirradiation $D_0=70$, $n=1.7$.

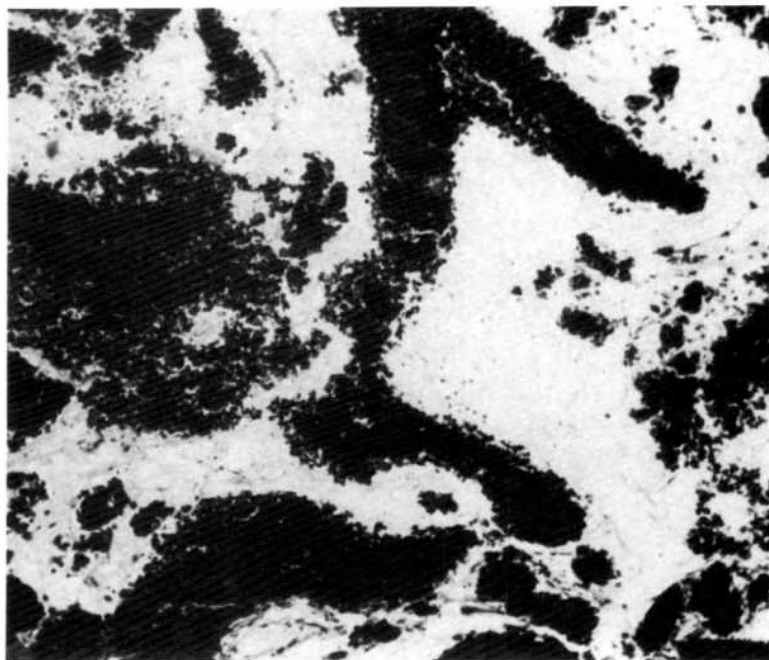


Fig. 3a Histopathological examination of the tumour shows marked calcification and tumour necrosis (Haematoxylin and eosin, $\times 30$).

of the 11 metaphases analysed one of the copies of chromosome 10 was missing. In addition all the cells contained structural alterations resulting in a number of marker chromosomes. A variable number of these markers were present in different metaphases. All

metaphases had a marker chromosome (M_1) which is produced as a result of breakage at the secondary constriction of chromosome 1 (1q-). M_2 was present in eight of 11 metaphases. This marker is derived from chromosome 2 by addition of chromosome

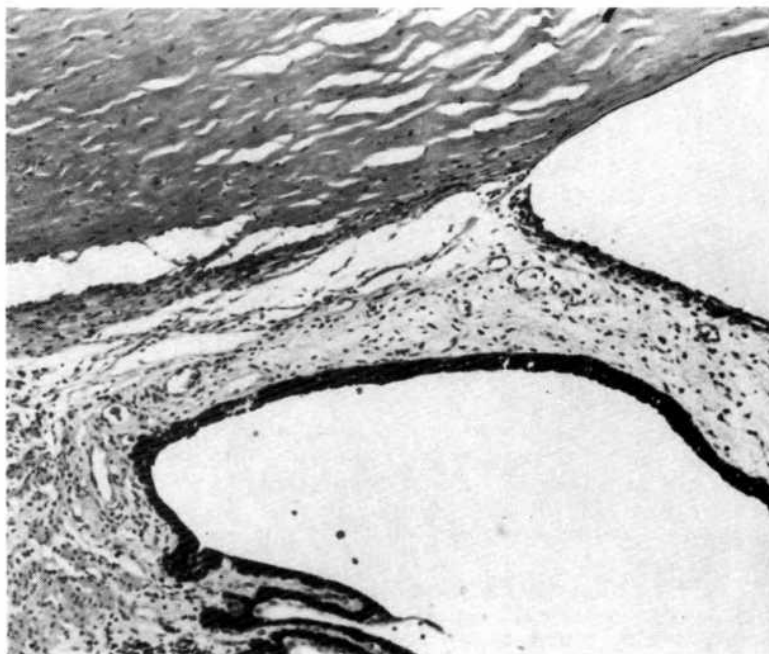
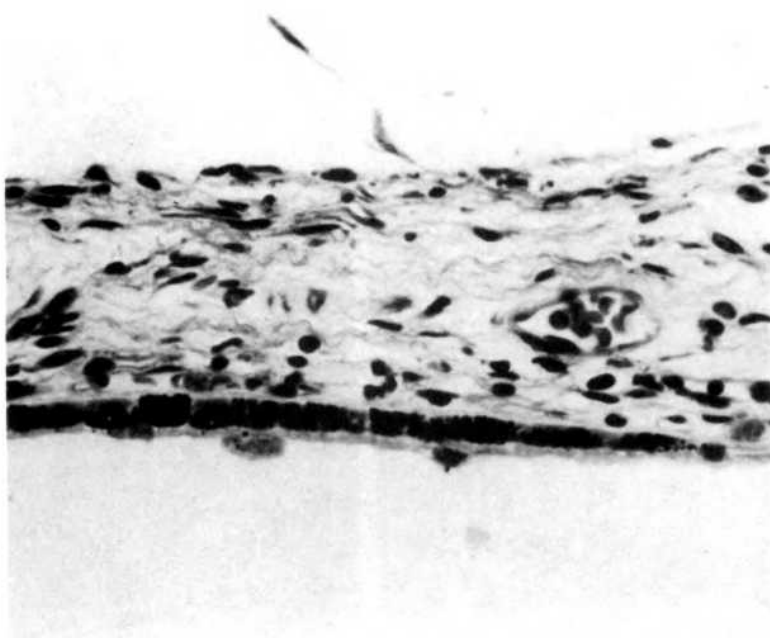


Fig. 3b A low power photomicrograph of the enucleated eye shows marked iris neovascularisation and closure of the filtration angle. (Haematoxylin and eosin, $\times 30$).

Fig. 3c Photomicrograph shows retinal changes, including preretinal fibrovascular membranes and extensive ganglion cell loss. (Haematoxylin and eosin, $\times 50$).



material in the distal half of chromosome 21. M_3 is derived from part of chromosome 7 to which additional material was added. M_4 probably represents virtually the entire chromosome 8 to which additional

material is added at the end of the long arm. M_5 is chromosome 9 with the major portion of the short arm deleted ($9p-$) and was observed in eight of 11 metaphases. M_6 is produced as a translocation be-

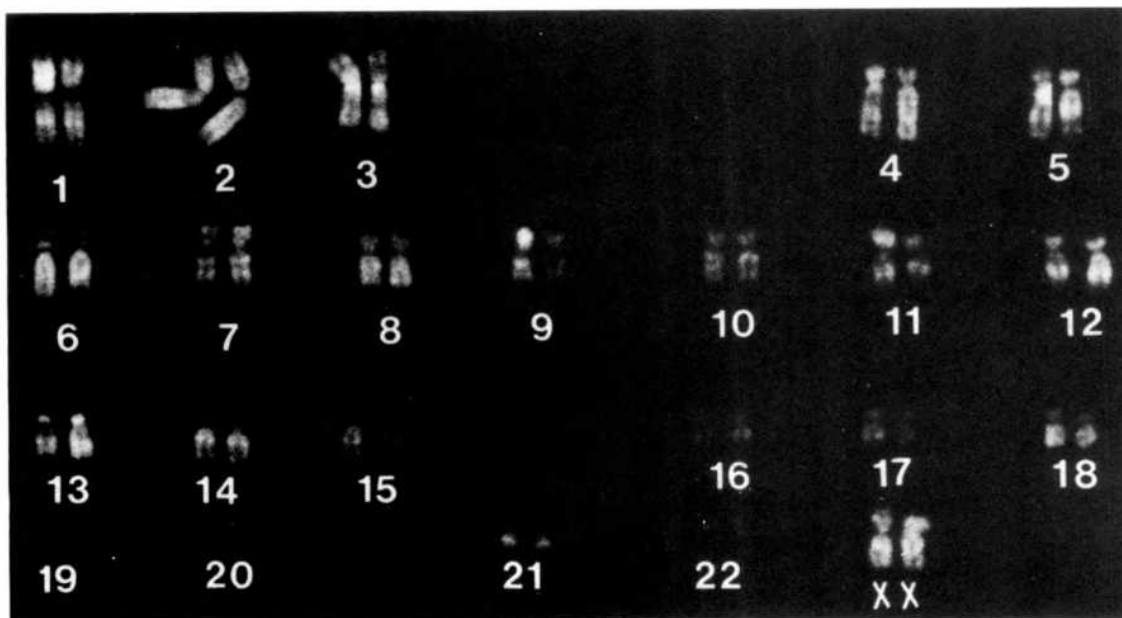


Fig. 4 A Q-banded karyotype of cultured fibroblasts obtained prior to radiotherapy. This is a normal human diploid female karyotype.

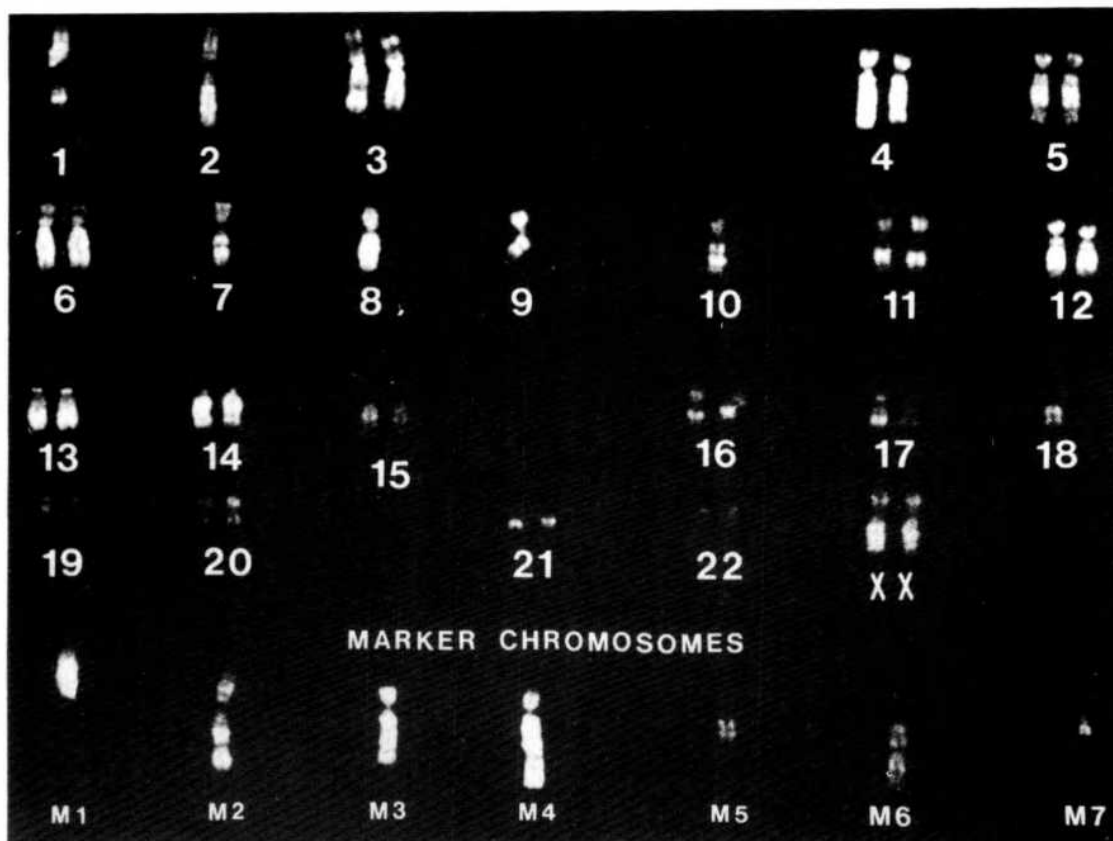


Fig. 5 A Q-banded karyotype of cultured fibroblasts following radiotherapy showing chromosome changes. This karyotype shows loss of one of each of chromosomes 1, 2, 7, 8, 9, 10, 18, and presence of marker chromosomes described in text.

tween chromosome 18 and the distal half of the long arm chromosome 1. M_7 is a small fragment. M_6 and M_7 were present in seven of the 11 metaphases. Fig. 5 shows a Q-banded based karyotype from B-814. Both markers M_3 and M_4 were present in seven of 11 metaphases.

Discussion

The clinical course and pathological findings in this case represent an unusually severe ocular and orbital response to radiation therapy. Rapidly progressive iris neovascularisation with associated angle closure glaucoma and preretinal fibrovascular proliferation occurred five months after bilateral irradiation for hereditary retinoblastoma. Subsequent histopathological examination revealed that the tumours were necrotic and conformed to the clinical and histological features of radiation and subsequent regression. Although neovascularisation is frequently observed in the eyes with untreated retinoblastoma and may be associated with retinal damage, its occur-

rence after radiation treatment in the doses given for this patient is unexpected.⁶⁻⁸ In this child it followed a fulminant course involving both iris and retina. Iris neovascularisation is a known ocular tissue response following irradiation, and there is a variety of clinical and experimental evidence that ionising radiation can cause retinal vascular occlusion, neovascularisation, and preretinal proliferative changes.⁹⁻¹³

This study is part of an ongoing investigation of DNA repair defects in patients with hereditary retinoblastoma. We have systematically obtained skin or conjunctival biopsies from these patients and performed x-ray survival studies, since a defect in DNA repair may be manifested by a decrease in survival to cytotoxic agents. The pretreatment x-ray survival curve parameters seen in fibroblasts from this patient are consistent with the moderate radiosensitivity noted in patients with hereditary retinoblastoma. The extreme radiosensitivity in the post-treatment fibroblasts is greater than that seen in any of our study patients with hereditary retinoblastoma and is near the range of radiosensitivity seen in

patients with ataxia telangiectasia.¹ Ataxia telangiectasia is an autosomal recessive disease characterized by a striking deficiency in the repair of x-irradiation induced DNA damage.

In spite of the fact that the pretreatment radiosensitivity ($D_0=111$) is consistent with the mean D_0 seen in fibroblasts from patients with hereditary retinoblastoma, this finding would not have predicted the extreme clinical reaction seen in this patient. The post-treatment radiosensitivity ($D_0=70$) is consistent with the severe clinical radiation reaction seen in patients with ataxia telangiectasia. Since the second fibroblast biopsy was obtained from an irradiated site, we may speculate that radiation damage may have been accumulated by cells exposed to the first dose which was expressed by the post-irradiation survival curve. This accumulation of x-ray damage may have accounted for the severe clinical reaction and the fact that extreme radiosensitivity was not seen in the preradiation experiments. This finding is consistent with our hypothesis that some patients with hereditary retinoblastoma may have a defect in the repair or accumulation of x-irradiation induced DNA damage which may reflect an underlying hypermutability and predispose to a second neoplasm.

When mammalian cells in culture are irradiated and a surviving clone selected from among the survivors, it has the same radiological characteristics as before radiation. Thus this case represents an unusual phenomenon of acquired radiosensitivity.¹⁴

The chromosome aberrations seen in this patient after radiotherapy are consistent with the effects of this agent on cells in vivo and in vitro. It is not known how these chromosomal aberrations relate to the development of the increased in-vitro radiosensitivity seen here. A slight increase in radiation-induced chromosome aberrations has been reported in cells from patients with hereditary retinoblastomas. It is disquieting that these severe chromoso-

mal aberrations exist after radiotherapy for a patient predisposed to radiation-induced malignancy.

Supported in part by grant EY01917 from the National Eye Institute.

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Eosinophils in corneas removed by penetrating keratoplasty

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SUMMARY One hundred consecutively submitted corneas removed by penetrating keratoplasty were studied histologically to determine the frequency in which eosinophils are found. In 20 corneas eosinophils occurred in densities ranging from 0.2 to more than 50 per high power field (HPF), and accounted for 1.5% to 100% of the total leucocytes counted. More than half of the corneal specimens containing eosinophils, including six of seven corneas having the highest eosinophil concentrations, were failed grafts. Because the concentration of eosinophils was in many cases beyond that attributable to non-specific vascular permeability, the existence of eosinophil chemotactic substances in the cornea is postulated.

The eosinophil has a poorly understood role in the inflammatory response and is typically associated with allergic disease and parasite infection.¹⁻⁷ Other than an occasional mention of eosinophils in corneal tissue in such conditions as onchocerciasis,⁸ few corneal diseases are known to be associated with eosinophilic infiltrates. It has been our observation, however, that eosinophils are relatively common in corneas removed by penetrating keratoplasty, and that these cases encompass a wide variety of corneal disorders. Since the validity of this observation and its significance are unknown, we undertook a study to determine the conditions associated with the presence and frequency of eosinophils in the cornea.

Material and methods

One hundred consecutively submitted corneal buttons removed by penetrating keratoplasty were studied. Each cornea was fixed in formalin and examined with a dissecting microscope. Focal corneal abnormalities (for example, ulceration, scar, etc.) were included in the bisected meridian. Corneas were embedded in paraffin and stained with haematoxylin and eosin and with the periodic acid Schiff reagent. Superficial and 0.5 mm deep corneal cross sections were examined at 100 × magnification for

the presence of eosinophils. Corneas in which one or more eosinophils were found were studied further.

The density of eosinophils was calculated from the total number of cells counted in five contiguous fields of 100 × magnification. The ratio of eosinophils to other leucocytes was based on total cell counts from the same five fields. In all cases counts were initiated in areas of greatest eosinophil concentration. The final anatomical diagnosis was determined by histopathological findings and clinical diagnosis.

The causes of graft failure were evaluated retrospectively. When it was impossible to establish the cause with certainty, we correlated the most significant clinical or anatomical abnormalities. The diagnosis of recurrent herpes keratitis was based on clinical criteria, viral culture, or the presence of herpetic giant cells in the epithelium of the failed graft.

Medical records from each patient with corneal eosinophils were reviewed. The following information was obtained: age, sex, race, past medical history, systemic and topical medications, history of allergies, and past ocular history. Complete blood counts with leucocyte differential were recorded from blood specimens drawn the day prior to surgery. Culture results and corneal scrapings were reviewed in all cases of corneal ulcer.

The association of categorical variables was analysed by the χ^2 method.

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Results

The final anatomical diagnoses of the 100 corneas removed by penetrating keratoplasty are listed in Table 1. The most common conditions necessitating

Table 1 *Diagnosis in 100 corneal buttons*

<i>Diagnosis</i>	<i>Percent of cases</i>
Corneal oedema	31%
Aphakic (14%)	
Pseudophakic (8%)	
Fuchs's dystrophy (9%)	
Failed graft	27%
Keratoconus	15%
Corneal ulcer	13%
Corneal scar	6%
Miscellaneous*	8%

*Herpes simplex keratitis (3), ocular pemphigoid (1), keratitis sacca (1), ocular leprosy (1), aniridia (1), and exposure keratopathy (1)

Table 2 *Diagnosis of 20 corneas with eosinophils*

<i>Diagnosis</i>	<i>Number of cases</i>
Graft failure	12
Corneal ulcer	3
Corneal oedema (pseudophakic and aphakic)	2
Exposure keratopathy	1
Keratopathy of aniridia	1
Keratoconus	1

surgery were corneal oedema (31%), graft failure (27%), keratoconus (15%), and non-healing corneal ulcer (13%).

Twenty corneas had one or more eosinophils present (Table 2). The diagnosis in these cases included graft failure (12), non-healing corneal ulceration (3), corneal oedema (2), exposure keratopathy (1), ocular leprosy (1), keratopathy of aniridia (1), and keratoconus (1). The density of eosinophils expressed as the number of cells per high power field (HPF) ranged from 0.2 to more than 50. The average number of eosinophils counted per cornea was 29.5. Eosinophils represented 1.8% to 100% of the total leucocytes in 14 corneas (Table 3). In six corneas differential counts could not be performed because necrosis prevented accurate identification of cells. Interestingly, eosinophils tended to be more resistant than other leucocytes to the effects of cellular degeneration. There was no correlation between the density of eosinophils and their ratios to other inflammatory cells. Three of the 20 patients had abnormal blood count differentials consisting of greater than 4% eosinophils (7%, 7%, and 11%). In none of these patients were there any other systemic conditions to account for the peripheral eosinophilia.

Eleven of the 27 failed grafts in this study had eosinophils, and six of the seven corneas with the greatest concentration of eosinophils were failed grafts. While 27% of the initial 100 corneas were failed grafts, 55% of the corneas containing eosinophils were graft failures ($p < 0.001$). The conditions

Table 3 *Cases with corneal eosinophils*

	<i>Case no.*</i>	<i>Final diagnosis</i>	<i>Density (no eosinophils per HPF)</i>	<i>Prevalence (no eosinophils per total leucocytes $\times 100$)</i>
Failed grafts	94	Pseudomonas ulcer	2.8	10%
	91	Proteus ulcer	>50	†
	52	Serratia ulcer	18.2	†
	18	Sterile ulcer	1.8	†
	53	Fungal keratitis	22.0	†
	8	Recurrent HSV keratitis	16.8	28.8%
	16	Recurrent HSV keratitis	7.6	32.6%
	19	Recurrent HSV keratitis	4.0	62.5%
	51	Recurrent HSV keratitis	12.8	100%
	43	Graft failure	2.4	50%
	45	Graft failure	1.0	33%
Native corneas	65	Aphakic bullous keratopathy	1.2	2.1%
	80	Aphakic bullous keratopathy	0.6	13%
	1	Pseudomonas ulcer	19.2	100%
	35	Pseudomonas ulcer	0.8	†
	42	Sterile corneal ulcer	3.6	56%
	27	Exposure keratopathy	0.8	1.8%
	11	Keratoconus	0.2	†
	46	Ocular leprosy with perforation	0.6	30%
	68	Keratopathy of aniridia	2.2	33%

*Twenty cases out of 100 consecutive, numbered cases examined †Unable to differentiate leucocytes accurately.

Table 4 Conditions associated with graft failures

Diagnosis	Number of cases with eosinophils (n=11)	Number of cases without eosinophils (n=16)
Recurrent herpes simplex	4	3
Bacterial ulcer	3	1
Fungal ulcer	1	0
Sterile ulcer	1	0
Failure with no known associated condition	2	7
Trauma	0	2
Exposure keratopathy	0	1
Keratitis sicca	0	1
Ocular hypertension	0	1

associated with graft failure are listed in Table 4. Three of the six grafts with large numbers of eosinophils occurred in patients who had had previous herpes simplex keratitis; two of these were 2-year-old boys with previous primary herpes simplex keratitis. The other three occurred in patients having non-healing corneal ulcers. The seventh cornea containing large numbers of eosinophils was from a patient who wore a contact lens and had an impending perforation due to pseudomonas infection. Although these seven cases appeared to have a substantially greater concentration of eosinophils, no statistically significant difference was observed between these groups because of the small number of cases involved ($p>0.10$).

Eosinophils were found in stroma adjacent to blood vessels in all but one cornea. In that one case eosinophils were present in an ulcer bed. Eosinophils in the corneas with ulcers were more concentrated near vascular channels than near ulcer defects.

One of the 20 patients had a known allergy characterised as seasonal rhinitis. No association was found between the presence of corneal eosinophils and topical or systemic medication, systemic disease, race, or sex. The majority of patients in this series lived in the south-eastern part of the United States within a 200-mile radius of New Orleans.

Discussion

One or more eosinophils were present in 20% of the corneas removed surgically in this series, a somewhat surprising observation, since corneal eosinophilia has rarely been reported. Detailed histopathological studies surveying corneal disease have not mentioned the eosinophil as an inflammatory component in the past.⁹⁻¹¹ Our study shows that eosinophils are often involved in corneal inflammatory disease and in many cases accumulate in concentrations beyond those attributable to non-specific increased vascular permeability.

Corneal eosinophilia is not associated with obvious allergic or parasitic disease in the vast number of cases that ultimately require keratoplasty in the United States. Although in this study eosinophils were present in a variety of corneal conditions, they were noted significantly more often in vascularised failed grafts than in native corneas ($p<0.001$). While graft failures accounted for 27% of the initial cases included in the study, they comprised 55% of corneas that contained eosinophils. It is interesting that two corneas with high concentrations of eosinophils occurred in failed grafts from 2-year-old children diagnosed as having primary herpes simplex keratitis.

Eosinophils undergo chemotaxis to a wide variety of stimuli, including components of the complement system, histamine, bacterial products, and factors elaborated by stimulated lymphocytes.¹⁻⁷ Although eosinophils are capable of phagocytosis, their more vital role is probably in dampening immediate hypersensitivity reactions by enzymatic degradation of chemotactic mediators.⁵ It is intriguing to speculate that this modulating effect may be operational in certain cases of corneal transplant rejection. One hundred and six years have passed since the ubiquitous eosinophil was identified by Ehrlich, and, although it is one of the most thoroughly described cells in the human body, its role in corneal disease remains totally obscure.

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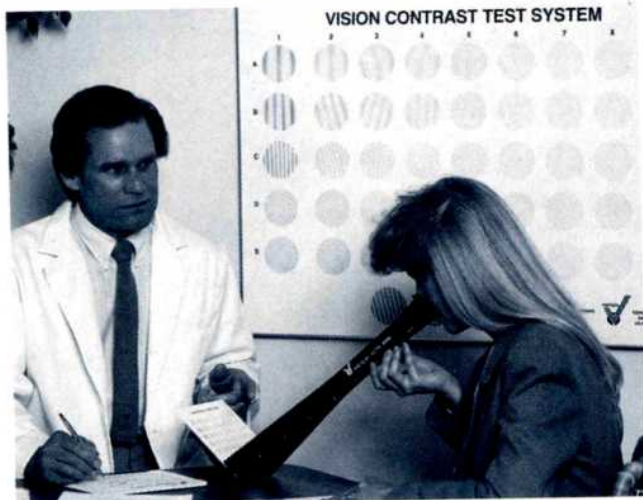
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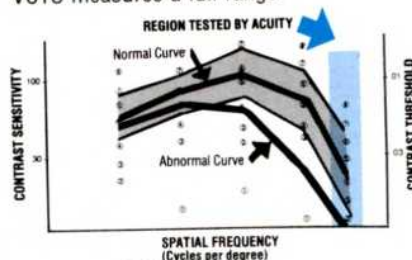
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Primary band-shaped spheroidal degeneration of the cornea: three cases from two consanguineous families

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SUMMARY Three cases of primary band-shaped spheroidal degeneration of the cornea from two consanguineous families are reported. In all cases vision deteriorated slowly, the deterioration beginning in childhood. Photophobia in childhood was also a common symptom, and two patients suffered from intermittent painful sensations. The occupational and environmental histories had no bearing on the cases. Histochemical study of the yellow, oily appearing deposits suggested that this material has a complex composition, with staining characteristics of both protein and acid-fast lipid.

Spheroidal degeneration of the cornea has been divided into two basic forms: primary and secondary.¹ The primary form is an aging process which affects only the peripheral cornea. The secondary form is constantly associated with other ocular pathology such as absolute glaucoma, phthisis bulbi, post-traumatic scars, and lattice corneal dystrophy. Climatic droplet keratopathy,² which is found in certain geographic regions where the eyes are exposed to climatic extremes, is categorised in the latter form. In both of these types of spheroidal degeneration of the cornea familial occurrence is extremely rare. This report describes three cases of primary band-shaped spheroidal degeneration of the cornea from two consanguineous families.

Case reports

CASE 1

A 42-year-old female was referred to us for corneal transplant in January 1983 because of progressively decreasing vision and recurrent painful irritation in both eyes for the past three years. Her vision had been slowly deteriorating since childhood. She had also been very photophobic during her childhood. She had not been examined by an ophthalmologist

until 31 years of age, when she was diagnosed as having bilateral corneal degeneration.

Occupational and environmental histories contributed nothing to the case. Her parents were first cousins and one of her brothers had the same corneal

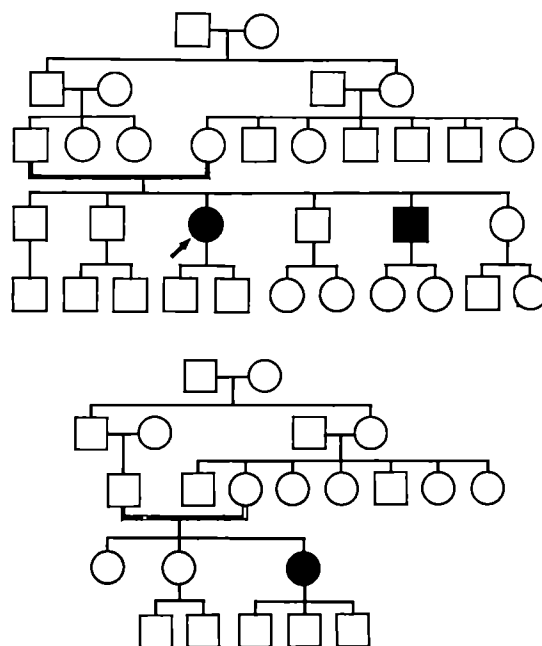


Fig 1 Family trees showing consanguinity. Top, family of cases 1 and 2. Bottom, family of case 3.

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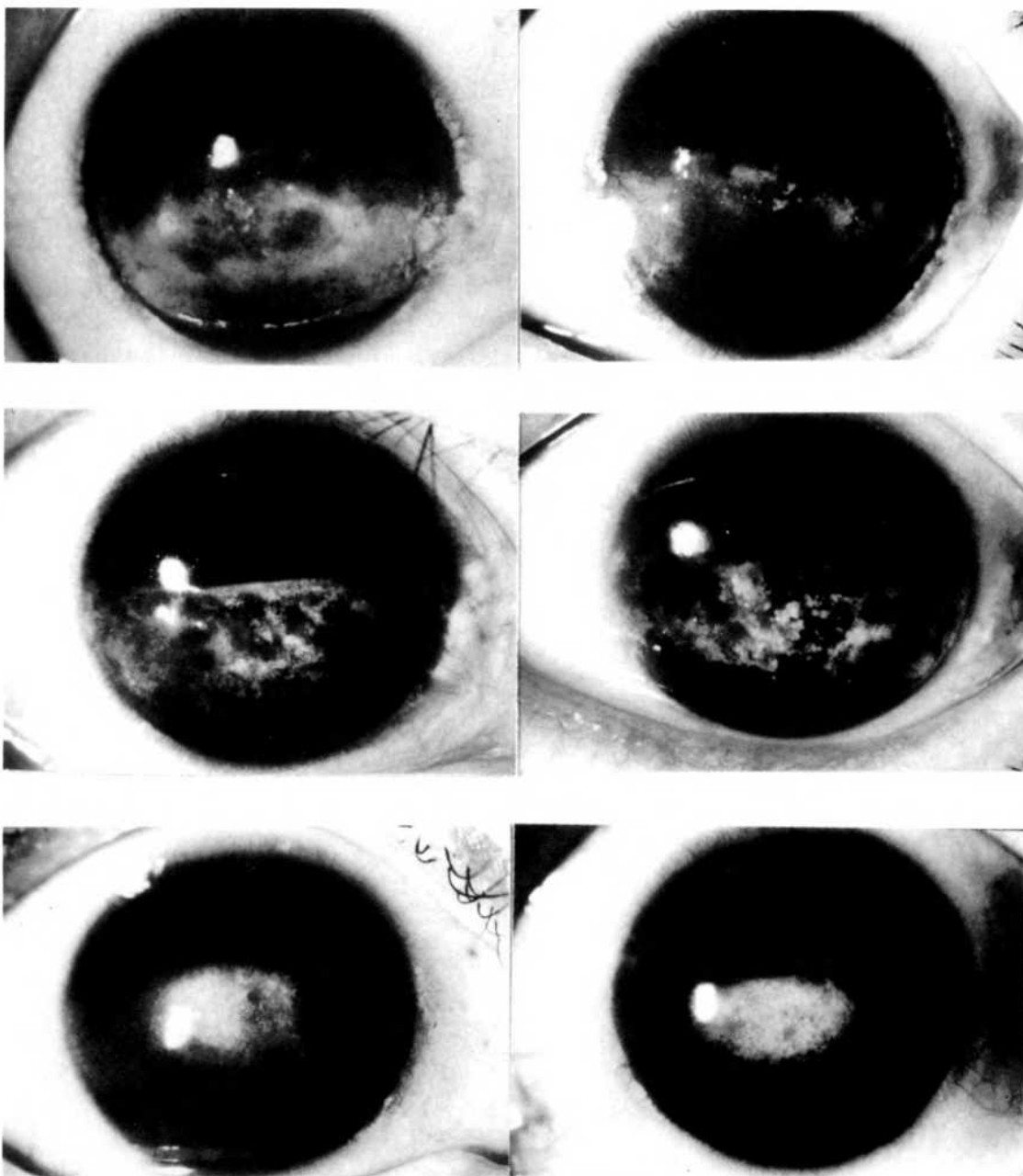


Fig. 2 Clinical appearance of the corneas. Top, case 1. Middle, case 2. Bottom, case 3.

condition in both eyes (Fig. 1, top). Ocular examination revealed corrected visual acuity of 20/200 and intraocular pressure of 12 mmHg bilaterally. Slit-lamp examination disclosed symmetrical band-shaped corneal opacities occupying the interpalpebral area in both eyes (Fig. 2, top). These

opacities consisted of yellow, globular, oily appearing droplets limited to the anterior stroma. Some globules raised the epithelium in the central cornea. Subepithelial vascular invasion into the opacified area from the nasal and temporal limbus was observed, as were yellow deposits in the horizontal

perilimbal conjunctiva. The right eye also contained a nasal pinguecula and the left eye a nasal pterygium. No other ocular abnormality was detected, and general physical and laboratory examinations gave normal results. Rotation autokeratoplasty on the left eye and lamellar keratoplasty on the right eye improved her corrected vision to 20/25 in each eye. The pinguecula of the right eye was also excised at the time of surgery.

CASE 2

A 35-year-old brother of the patient in case 1 was examined in October 1983. His best corrected vision

was 20/100 OD and 20/50 OS. Intraocular pressure was 8 mmHg OU. A slit-lamp examination disclosed band-shaped corneal opacities similar to those of case 1 in both eyes (Fig. 2, middle). However, the yellow globules were larger than those of case 1, especially in the central cornea. Horizontal perilimbal yellow deposits and pingueculae were present bilaterally. His vision had been poor since childhood and had deteriorated slowly. He had also been photophobic during his childhood but had never suffered from painful irritation. Occupational and environmental histories were unremarkable, and in general he had been healthy.

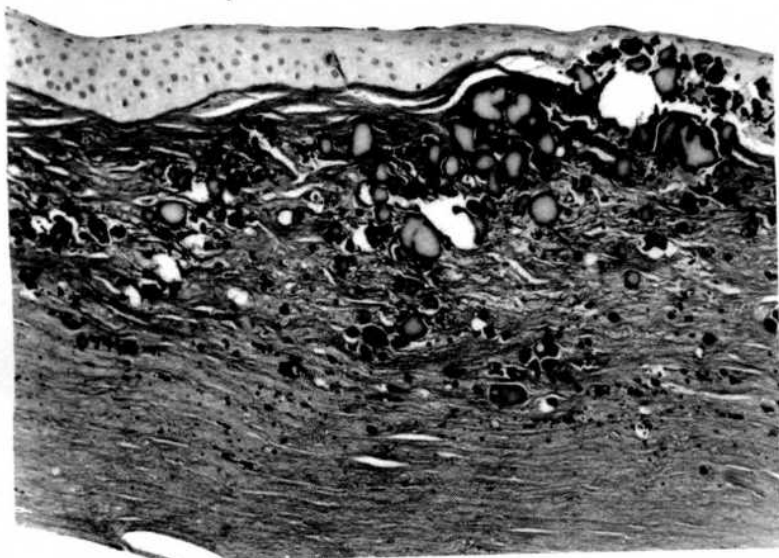
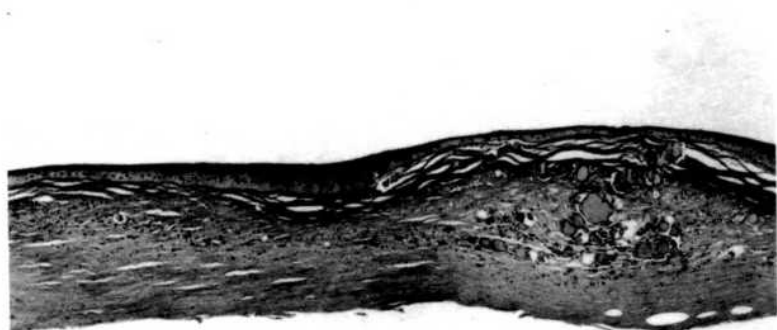


Fig. 3 Histological section of the cornea of case 1. (Top, haematoxylin-eosin, $\times 53$. Bottom, phosphotungstic acid/haematoxylin, $\times 132$).

CASE 3

A 35-year-old female was referred for corneal transplant in July 1982 because of slowly progressive blurring of vision and intermittent painful irritation in both eyes for the past 10 years. Her vision had been poor since childhood, and she had a history of photophobia and epiphora as a child. Her parents were first cousins, but no other family member was affected with the same corneal problem (Fig. 2, bottom). Ocular examination revealed corrected

visual acuity of 20/200 OD and 20/40 OS. Intraocular pressure was 17 mmHg in each eye. Slit-lamp examination revealed bilateral symmetrical band-shaped corneal opacities occupying the interpalpebral area in both eyes (Fig. 2, bottom). These opacities consisted of fine, yellow, oily appearing globules limited to the anterior stroma. Yellow globular deposits were also observed in the horizontal perilimbal conjunctiva. Subepithelial vascular invasion was detected in every quadrant but was most prominent

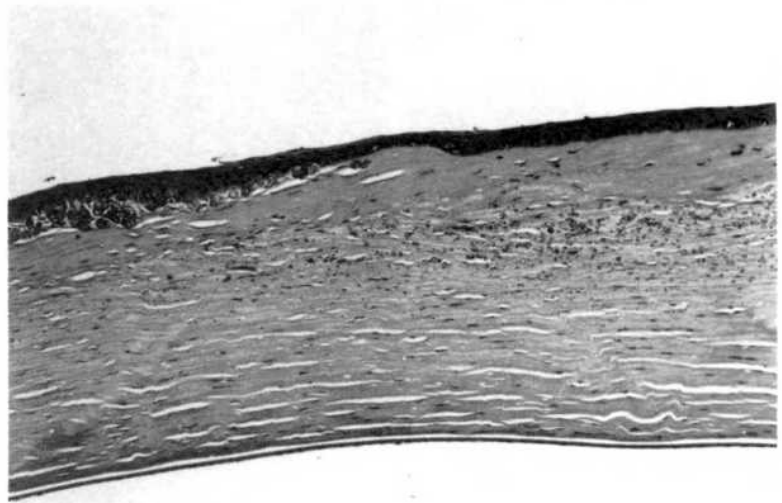
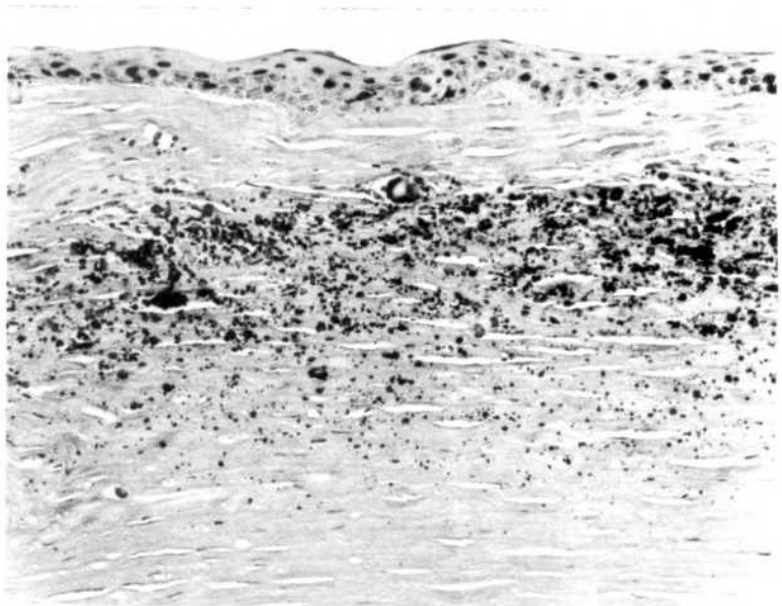


Fig. 4 Histological section of the cornea of case 3. (Top, haematoxylin-eosin, $\times 83$. Bottom, Ziehl-Neelsen, $\times 166$).



from the horizontal limbus into the opacified area. No other ocular abnormality was detected, and general physical and laboratory examinations were normal. Penetrating keratoplasty was performed on the right eye on 20 August 1982. Allograft rejection occurred one month after surgery but was successfully treated by systemic and local steroid therapy. The corrected vision improved to 20/25 in the right eye.

PATHOLOGICAL FINDINGS

The histological sections of the corneas from cases 1 and 3 showed eosinophilic globular deposits of various sizes located primarily in the anterior stroma (Figs. 3 and 4, top). These globules stained positively with phosphotungstic acid haematoxylin (Fig. 3, bottom) and Ziehl-Neelsen stains (Fig. 4, bottom). Periodic acid Schiff and luxol fast blue stains were weakly positive. Verhoeff's elastin stain was positive, but this response was unaffected by elastase digestion. Congo red, von Kossa, Mallory's aniline blue, van Gieson elastic, resorcin-fuchsin, orsein, alcian blue, oil red O, Sudan black B, Nile blue, Ralph's

method for haemoglobin, and iron stains were all negative. The globules of unstained sections were autofluorescent. Immunohistological studies using the peroxidase anti-peroxidase method showed that these deposits did not react to anti-human-keratin antibody. The epithelium varied in thickness, and in some areas there was remarkable thinning associated with elevation by the globular deposits. Bowman's layer was destroyed, and the superficial stroma had lost the normal parallel arrangement of collagen fibres. Sections of the pinguecula from case 1 showed similar globular deposits in degenerated elastotic subepithelial tissue.

Corneal tissue from case 1 was fixed in 4% glutaraldehyde and examined electron microscopically. The stromal deposits were markedly electron dense and structureless (Fig. 5). Most of the small globules were round or oval in shape and the larger ones were irregular. They were always extracellular. Some globules showed granularity at their edges, but others had sharp borders. Apparently normal collagen fibrils surrounded some globules, but most were adjacent to degenerating collagen. There was

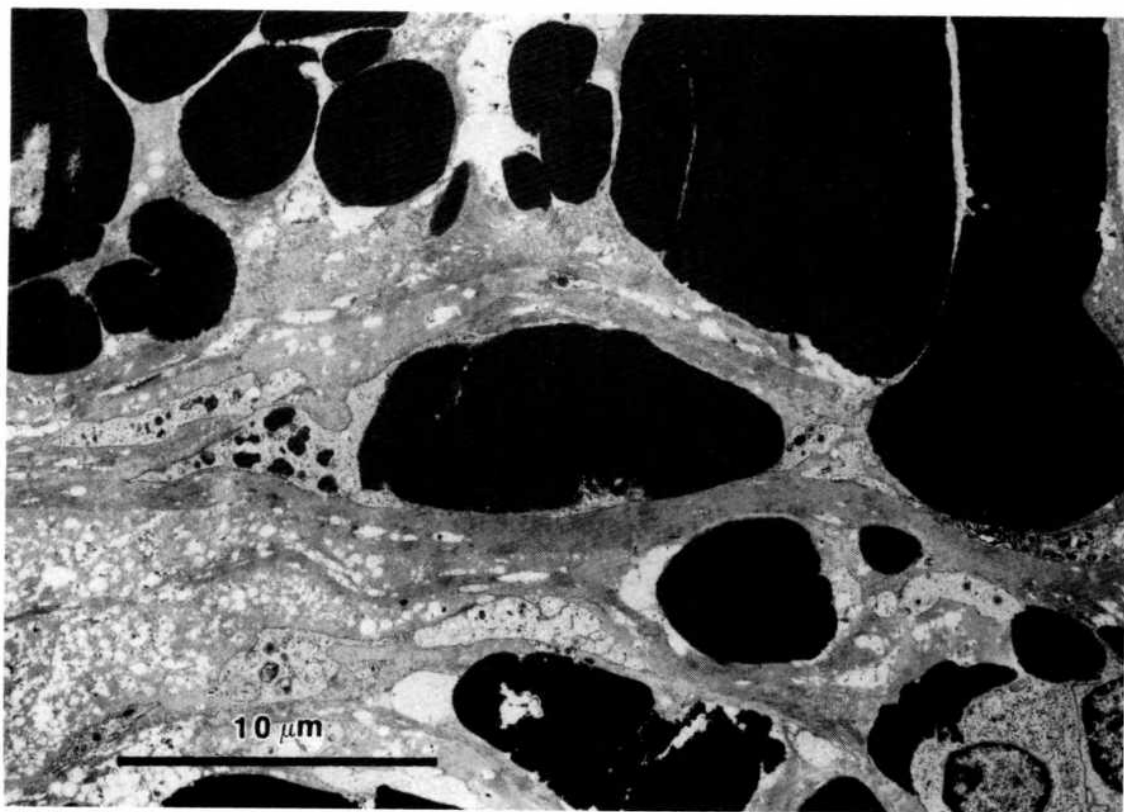


Fig. 5 Transmission electron micrograph of the cornea of case 1 showing the absolutely structureless electron dense deposits of various size in degenerated stroma. ($\times 4200$).

also vacuolisation of Bowman's layer and superficial stroma. A few keratocytes contained large electron dense bodies but not any material that resembled the stromal deposits. X-ray microanalysis performed with a JEOL 1200EX electron microscope showed no significant differences between the deposited material and the surrounding area.

Discussion

The corneal degeneration characterised by deposits of yellow, oily appearing globules has been described under a variety of terms,³ with spheroidal degeneration being most widely used. There is a variety of situations in which this type of disorder can occur, and complete clinical patterns and histological characteristics are not consistent in previous reports.¹⁻⁴ Nevertheless, there has been agreement that these globular deposits do not constitute a separate disease entity but represent a response of the cornea to various stimuli.³⁻⁴

Fraunfelder and colleagues^{1,3} divided this condition into three basic forms: (1) the primary corneal type associated with increasing age; (2) the secondary corneal type associated with significant pre-existing pathology; and (3) the conjunctival type. The primary corneal type in this classification is not a rare occurrence but never involves the central cornea. Our cases cannot be classified by these criteria. All three patients were rather young, had band-shaped depositions involving the central cornea, and had no history of other ocular diseases or of unusual exposures to extreme environments.

Klouček⁴ and Meisler *et al.*⁷ reported cases of familial band-shaped spheroidal degeneration. Klouček's cases were patients in the fourth and seventh decade but had noted their deterioration of vision in the second or third decade of life. The cases of Meisler *et al.* were three brothers, and two of them were in the third decade of life. The changes in the central cornea of the youngest brother were different from the yellow globular depositions. Pedigrees of the families of Meisler *et al.* and ours suggest an autosomal recessive inheritance of this condition.

Spheroidal degeneration has been reported as a secondary phenomenon in patients with lattice dystrophy,⁶ a primary corneal amyloidosis. Three cases of primary band-shaped keratopathy have been reported in consanguineous families whose relatives had gelatinous drop-like dystrophy, another form of corneal amyloidosis.¹⁶⁻¹⁸ The clinical and histological findings in these latter cases agree remarkably with ours, though they were not identified as spheroidal degeneration. In one of these three cases of band-shaped keratopathy the patient developed gelatinous

drop-like dystrophy only after a superficial keratectomy had been performed.¹⁸

The aetiology of these globular deposits is controversial. Klintworth⁴ has noted their association with conjunctival elastosis (pingueculae). Two of our cases also had pingueculae or pterygium in both eyes. Garner *et al.*⁹ demonstrated the pseudoelastic nature of these materials by positive staining with Verhoeff's stain and a lack of response to elastase digestion and other elastic stains. The same staining results were obtained in our cases. The histochemical data from our cases further suggest that the material in the globules has a complex composition, with staining characteristics of both protein and acid-fast lipid. Electron microscopy and x-ray analysis of our cases did not reveal any new information about the origin or characteristics of these globules.

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Sequential antibody changes following ulcerative herpetic keratitis

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SUMMARY Blood and tear levels of immunoglobulins against herpes simplex virus (HSV) were examined in 28 patients with dendritic keratitis over a period of 28 days. By means of an indirect micro-immunofluorescent technique blood and tear HSV IgG were detected, but neither circulating HSV IgM nor local HSV IgA were found. Over a four-week interval non-diagnostic fluctuations of HSV IgG occurred in most patients, though seven (25%) developed a rising blood IgG titre. Tear IgG appeared to be an exudate from blood. HSV was isolated from 68% of corneal swabbings and 11% of conjunctival swabbings. This study provides guidelines for laboratory testing in recurrent herpetic keratitis.

Initial immune responses during primary herpes simplex virus (HSV) ocular infection include lymphocyte sensitisation with macrophage activation and the development of specific HSV IgM antibodies followed by HSV IgG and IgA antibodies. Subsequently the IgG titre may persist for a long period and is useful in seroepidemiological surveys for estimating a population's exposure to HSV. But despite circulating HSV antibodies some individuals later develop recurrent keratitis. To determine if recurrent herpetic eye disease may be associated with an anamnestic humoral immune response we have prospectively evaluated blood and tear HSV antibody titres from patients with dendritic keratitis.

Materials and methods

Specimen collection. Clinical specimens were collected from patients with typical dendritic corneal ulceration attending Moorfields Eye Hospital, London. Whole blood and tears were collected on cellulose sponges¹ from each patient on the day of presentation, after 14 days, and after 28 days. At the time of first examination, after the eye was anaesthetised with benoxinate solution conjunctival specimens were taken by rubbing a dry cotton-tipped swab across the everted upper and lower conjunctivae. Corneal epithelial debridement was performed with a sterile cotton-tipped applicator removing the

loosened corneal epithelial cells at the ulcer edge. Patients received 3% acyclovir ointment five times daily and 1% atropine eye drops twice daily until the corneas were healed.

Viral isolation. Conjunctival and corneal swabbings were placed into individual capsules containing 1.2 ml of 2SP transport medium² with 3% fetal calf serum, stored in a liquid nitrogen refrigerator (-180°C), and transferred to the laboratory, where they were stored in a -70°C refrigerator. Each clinical specimen was inoculated into two tubes containing monolayers of HEp 2 cells in accordance with the method described elsewhere.^{3,4} Viral isolates were identified by a fluorescent antibody technique.

Serology. Each saturated sponge containing whole blood or tears was placed in a tightly stoppered dry capsule, transferred to the laboratory, and stored at -20°C . Blood and tear specimens were tested for type specific antibodies to HSV by an indirect micro-immunofluorescent technique.⁵ HSV IgG and IgM were sought in blood at starting dilutions of 1:16 and 1:8 respectively. Tears were tested for HSV IgG and IgA at a starting dilution of 1:8. Blood was also tested for HSV antibodies by the complement fixation technique.

Results

Twenty-eight patients with dendritic keratitis were studied, 11 females and 17 males, with an average age of 47 years (SD 15, range, 16-74). All healed within 10 days; four patients (cases 5, 12, 23, and 27) later

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developed disciform keratouveitis. HSV type 1 was isolated from 3 (11%) of the conjunctival swabbings and from 19 (68%) of the corneal debridement samples (Table 1). No HSV type 2 was isolated from these patients. The presence of a positive culture was not statistically associated with any clinical factor, including the duration of symptoms.

Serological results for each patient are listed in Table 1. Antibodies in every case were specific for HSV-1, although low-level cross reactions with HSV-2 did sometimes occur. Type specific HSV IgM was not detected from any blood specimen. The reciprocal geometric mean titres of circulating HSV-1 IgG were 13 on day 0, 9 on day 14, and 8 on day 28. Seven (25%) of the patients developed a fourfold rise in circulating HSV IgG during the one-month follow-up period. Seventeen (61%) of the patients had no detectable blood HSV IgG on at least one of the three sampling days.

Type specific HSV IgA was not detected in the tears from any patient. HSV IgG was detected with a reciprocal geometric mean titre of 4 at day 0, and 0.5 and 0 at days 14 and 28 respectively. The level of HSV IgG was always equal to or less than the corresponding blood HSV IgG. Only one patient showed a fourfold rise in tear antibody titre, and this was from

a patient who also had a rise in blood antibody. Complement fixing HSV antibody was detected in 27 patients, and no significant fluctuation was noted (Table 1).

Discussion

Early work on the antibody response following HSV infection provided the first clues that the virus can persist endogenously after the primary infection. Burnet and Williams⁴ postulated that the latent virus conveys 'a constant or intermittent antigenic stimulus which maintains a circulating antibody at a high level.' Prospective studies on the antibody response during the four weeks following recurrent mucocutaneous herpetic disease confirmed that circulating HSV antibody levels usually remain relatively constant,⁷⁻¹² though significant fluctuations of a fourfold or greater rise in antibody titre occurred occasionally.^{7*} Moreover, asymptomatic recurrent HSV shedding does not usually stimulate a rise in antibody titre,¹³ but endogenous viral reactivation can sometimes contribute to increases in IgG, IgM, or IgA titres.¹⁴ Similar studies on herpetic ocular disease showed that serological testing is useful to confirm a primary infection but noted that 'recurrent attacks of

Table 1 Relation of HSV isolates to blood and tear reciprocal antibody titres in patients with dendritic keratitis

Patient	Age	Sex	Previous attack	Duration of symptoms (days)	Conjunctival culture	Corneal culture	HSV-1 blood IF IgG on day			HSV-1 tear IF IgG on day			HSV blood CF Ig on day		
							0	14	28	0	14	28	0	14	28
1	69	F	Y	1	—	—	0	0	0	0	0	0	20	40	40
2	64	F	N	3	—	+	0	0	16	0	0	0	20	40	20
3	55	M	Y	2	—	+	0	0	32	0	0	0	20	20	20
4	16	F	N	1	+	+	0	16	0	0	0	0	0	0	0
5	60	M	Y	1	—	—	0	16	16	0	0	0	20	20	10
6	42	M	N	2	—	+	0	32	16	0	16	0	20	20	10
7	74	M	Y	1	—	—	0	64	32	0	0	0	20	40	20
8	31	M	Y	1	—	+	16	0	0	16	0	0	40	40	40
9	36	F	Y	1	—	—	16	16	16	8	0	0	20	20	20
10	40	M	N	1	—	+	16	16	16	0	0	0	20	20	20
11	53	M	Y	1	—	+	16	32	0	16	0	0	80	80	80
12	56	M	Y	1	—	+	16	32	32	8	0	0	20	20	20
13	40	M	N	2	—	+	16	32	32	16	0	0	80	80	80
14	73	M	Y	2	—	+	16	64	64	0	0	0	80	80	80
15	59	F	Y	1	—	—	32	0	0	0	0	0	10	10	10
16	41	F	N	2	—	+	32	0	0	0	0	0	40	40	40
17	45	M	Y	1	—	+	32	0	16	0	0	0	20	20	10
18	54	F	Y	2	—	+	32	0	16	16	0	0	80	80	40
19	54	F	N	2	—	+	32	16	16	0	0	0	10	10	10
20	27	M	N	1	—	+	32	16	16	0	0	0	40	40	40
21	23	F	Y	1	—	—	32	32	16	0	0	0	20	20	20
22	53	M	Y	2	—	—	32	64	32	8	0	0	40	40	40
23	35	F	N	2	+	+	64	0	64	0	0	0	40	40	40
24	42	M	Y	1	—	+	64	32	0	8	0	0	40	40	40
25	70	M	N	1	+	+	64	32	0	0	0	0	20	20	20
26	42	F	N	1	—	+	64	32	0	8	0	0	80	80	80
27	40	M	Y	1	—	—	64	32	16	0	0	0	20	20	20
28	45	M	Y	1	—	—	128	16	16	8	0	0	160	80	80

Y=yes N=no +=Positive -=Negative IF=immunofluorescent CF=complement-fixing

herpetic infection are not associated with changes in the antibody level before, during, or after these episodes.¹⁵

In the present series 28 patients with dendritic keratitis were studied over four weeks. Blood and tear HSV IgG could be detected, but neither circulating HSV IgM nor local HSV IgA were found. Seven (25%) of the patients developed a fourfold rise in blood HSV-1 IgG titre during the follow-up period. One patient had no detectable blood HSV-1 antibody at any time, and 61% had no detectable tear HSV-1 antibody. Because the tear IgG level was equal to or less than the corresponding blood IgG titre, tear antibody appears to be an exudate from blood. Cross reacting antibodies to HSV type 2 were occasionally detected.

The results of this study may provide guidelines to the role of laboratory testing in herpetic keratitis. Firstly, while recurrent herpetic keratitis does not usually cause a rise in antibody titre, 25% of our patients with dendritic keratitis did develop a significant elevation of immunofluorescent IgG antibody. Secondly, circulating HSV IgM was not detected following dendritic keratitis. An elevated HSV IgM titre would be more suggestive of a primary infection than a recurrence, though some studies have found individuals with a persistent level of HSV IgM antibodies between or at the time of clinical recurrences.¹⁶ Thirdly, after they had been treated, some seropositive individuals reverted to apparent seronegativity as measured by the indirect micro-immunofluorescent technique, though complement-fixing antibodies persisted. Prior HSV exposure may need to be assessed either by different serological assays or by repeated testing on an individual. We cannot explain why antibody levels occasionally became undetectable following an initially positive test in some patients. Fourthly, local production of HSV IgA is not apparently involved in recurrent keratitis, though other workers have found a rising tear IgA titre following dendritic keratitis.¹⁷

Finally, viral isolation from corneal debridement swabbings is useful to confirm the presence of HSV in patients with dendritic keratitis. Our study suggests that HSV can be isolated from approximately two-thirds of patients with dendritic keratitis and that corneal epithelial debridement swabbings are more sensitive than conjunctival swabbings in detecting HSV.

The host factors that lead to viral shedding, clinical recurrences, and recovery remain obscure. Antibodies may be involved in controlling the latent HSV in the trigeminal ganglion¹⁸ but do not appear to confer protection against recurrences. Furthermore, while antibodies can combine to Fc receptors on virus infected cells, HSV spreads by direct cellular contact

prior to the expression of sufficient virus-specific surface antigens. Cell-mediated immunity and production of interferon and other lymphokines may be more important in limiting the spread of HSV, and antiviral therapy could affect these immune responses. Further work remains to determine the effects of humoral and cellular immunity in the pathogenesis of recurrent herpetic ocular disease

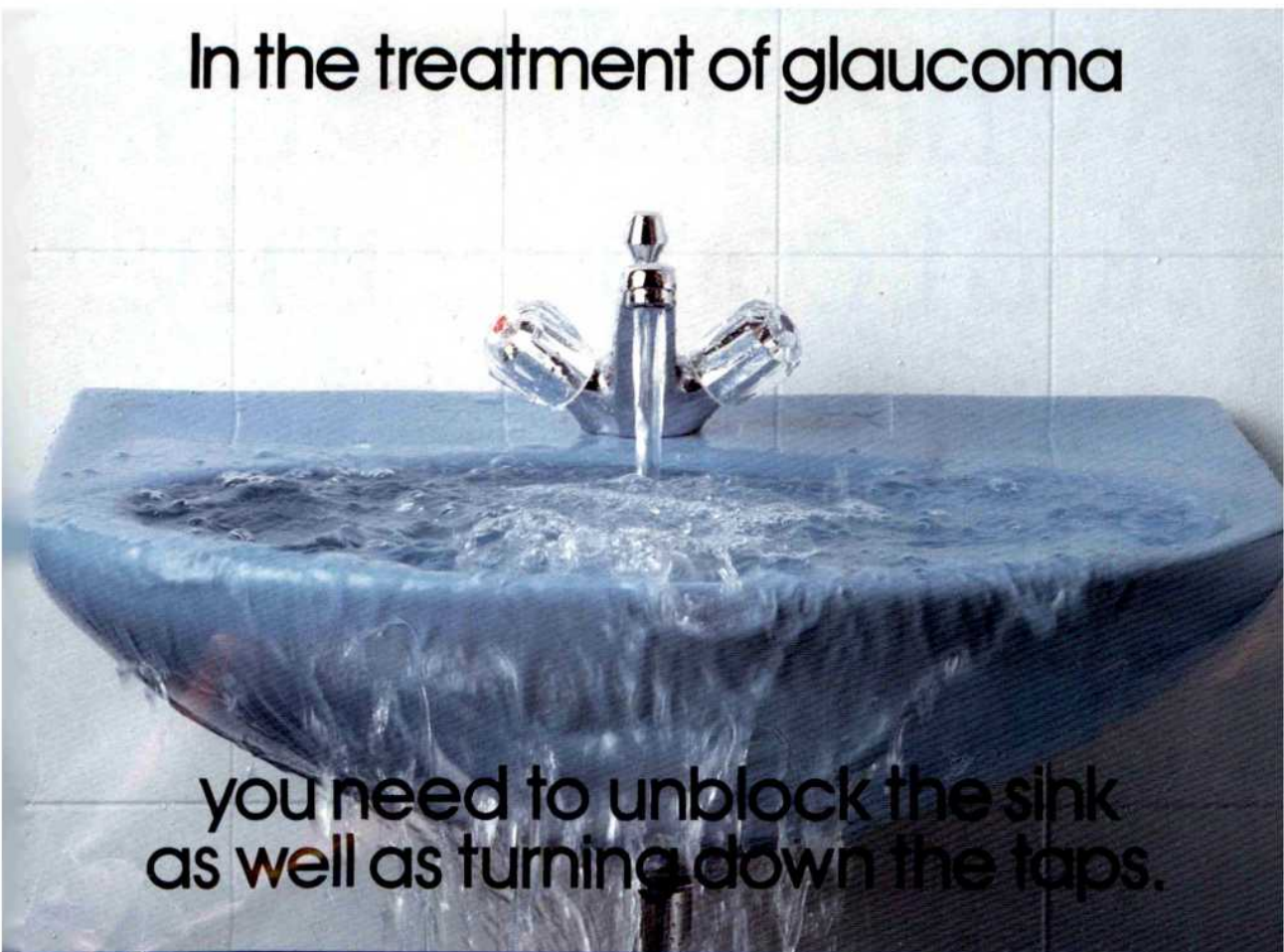
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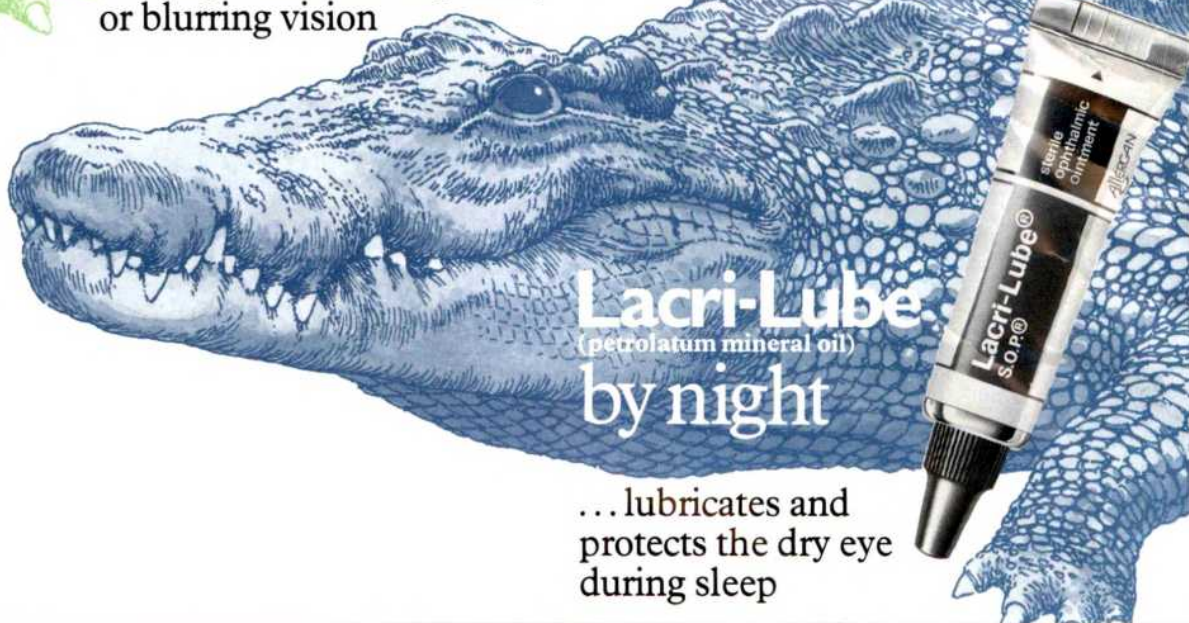
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Keratomalacia on a 'healthy diet'

JANE OLVER

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SUMMARY The case is described of a 39-year-old man with previously undiagnosed chronic schizophrenia and with bilateral keratomalacia secondary to his bizarre diet. He presented with a perforation of the right cornea which required an emergency penetrating keratoplasty. The difficulties of clinical management of a patient with an overt psychosis and the use of serum retinol levels to monitor treatment are described. Causes of vitamin A deficiency seen in Great Britain are discussed.

Vitamin A deficiency is common throughout the world in general but is rarely seen in the United Kingdom. It is closely associated with protein energy malnutrition,¹ and it arises when the diet contains practically no whole milk or butter and very limited amounts of fresh vegetables or fruit, therefore lacking both retinol and carotenes. The disease is almost unknown in Europe today, but an outbreak in Denmark during the first world war is instructive.^{2,3} It occurred despite the fact that Denmark had very large dairy herds, so that ample supplies of Vitamin A should have been available. However, because most of the butter was exported to Germany, the poor could obtain only separated milk and lived on a diet of oatmeal gruel and barley broth. Some 700 children were affected of which 400 had keratomalacia. In 1918 a weekly ration of butter was issued and the disease disappeared.

A case of bilateral keratomalacia and endophthalmitis with a right perforated cornea is described. The patient was a previously undiagnosed chronic schizophrenic. He had been observing a strict vegan diet for seven years, resulting in severe nutritional deficiencies (a vegan is an extreme vegetarian, who consumes no animal food or dairy products whatever).

Case report

History and examination. This 39-year-old Caucasian male was admitted as an emergency with a marginal perforation of the right cornea. He had been 'worried' about his eyes for the previous five days, complaining of photophobia, watering, discharge,

and deterioration of visual acuity. He denied any problems with night vision but admitted that for four months he had become a recluse, staying in his room with the lights off and finding his way around by touch. During the five days prior to presentation he described two episodes of profuse watering from the right eye.

His general appearance was unkempt and emaciated and he appeared severely malnourished. His visual acuity was reduced in each eye to counting fingers. Examination was hampered by his excited and uncooperative state as well as his severe photophobia and discomfort. He refused to be examined at the slit-lamp. His lids were erythematous and oedematous, with a marked purulent discharge. His conjunctivae were chemosed and severely injected, with dry keratinised epithelium typical of xerophthalmia. The corneae were of ground glass appearance. The right cornea had a superior marginal perforation with an iris prolapse, a flat anterior chamber, and a hypopyon. The left cornea had a similarly placed desmetocoele, containing sloughed material, a formed anterior chamber, and a hypopyon. There was a second smaller ulcer near the centre of the left cornea. The above findings precluded a clear fundal view.

General examination revealed widespread skin lesions which were pigmented and keratinised, with follicular plugging.

His mental state was assessed by the psychiatrists, who confirmed a diagnosis of chronic schizophrenia, with 'knight's move' thought disorder and autochthonous delusions.

Further inquiry revealed that he had eaten a strange diet. He believed that poisons entered the

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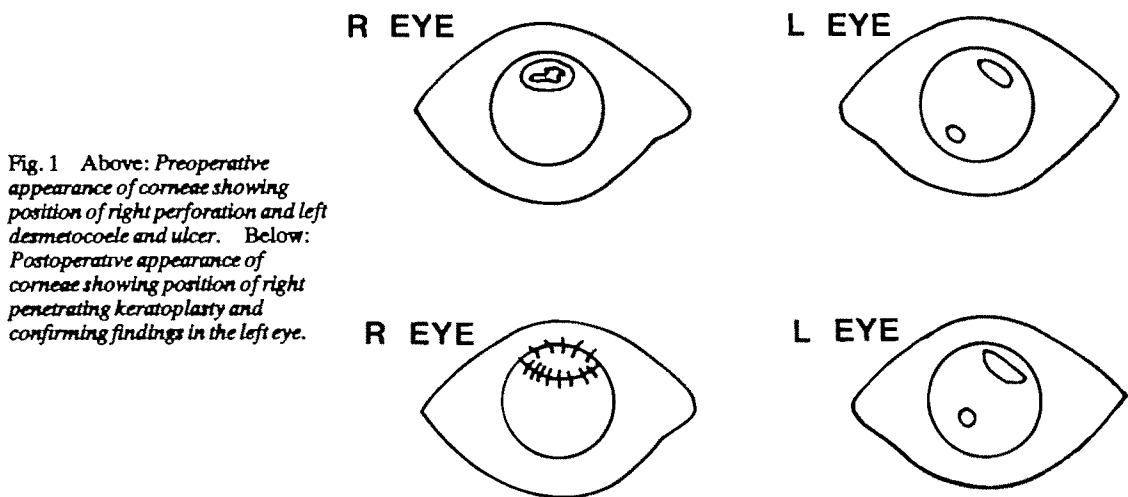


Fig. 1 Above: Preoperative appearance of corneas showing position of right perforation and left desmetocoele and ulcer. Below: Postoperative appearance of corneas showing position of right penetrating keratoplasty and confirming findings in the left eye.

body in our food and that a 'good' diet was essential to maintaining good health. He had therefore become a vegetarian in the 1960s and in 1977 had become a strict vegan. In addition to excluding all animal and dairy produce he had completely avoided even vegetables and fruit for seven years. His diet consisted of partially cooked brown rice, pulses, and sprouting alfalfa, all very low in vitamin A and carotenoids. He believed that this was a well balanced diet and included all essential nutrients. On admission he weighed 55 kg, and after two months' inpatient stay on a high protein, high calorie diet he weighed 75.5 kg.

Immediate management. Examination under anaesthetic confirmed our earlier findings. We carried out an emergency right upper segment penetrating keratoplasty. The edges of the ulcer around the area of perforation were very friable and had to be excised to allow secure suturing of fresh donor material to make good the defect (Fig. 1).

Investigations. Culture of conjunctival swabs from each eye grew *Haemophilus influenzae* and commensals. Serum retinol, β -carotenoid, retinal binding protein, and prealbumin were extremely low. There was evidence of generalised malnourishment with a very low vitamin D and fasting triglyceride and cholesterol levels. Vitamin B₁₂, vitamin C, zinc, and copper were all at the lower limit of normal (Table 1). Other workers have suggested that electroretinogram (ERG) and dark adaptation tests are useful in monitoring this condition (see Discussion), but unfortunately our patient would not co-operate with any of these investigations. Nor would he allow us to photograph him.

Treatment. Postoperatively the endophthalmitis was treated with systemic ampicillin and flucloxacillin

orally, 500 mg of each four times a day, and intensive topical antibiotics, gentamicin and chloramphenicol eye drops hourly initially, with atropine cycloplegia. He required three subconjunctival injections of methicillin and gentamicin on three consecutive postoperative days. Four days after operation topical steroids were introduced for uveitis and vitritis. He remained on systemic antibiotics for three weeks, and topical treatment was gradually reduced over eight weeks.

A regimen of vitamin A replacement therapy was started, and the serum levels monitored at intervals (Table 2, Fig. 2). After much persuasion he agreed to take a high protein, high calorie vegan diet with additional multivitamins.

Progress. The patient's eyes rapidly improved on vitamin A replacement therapy. The corneal haze cleared over two weeks. Five months after presenta-

Table 1 Biochemical investigations on admission

	Serum level	Normal range
Retinol	0.56 μ M	2.13–4.64 μ M
Carotene	0.20 μ M	0.6–4.64 μ M
Retinol binding protein	16 mg/l	36–84 mg/l
Pre-albumin	70 mg/l	269–405 mg/l
Vitamin D (25-hydroxycholecalciferol)	0.3 ng/l	8–50 ng/l
Vitamin B ₁₂	170 ng/l	120–600 ng/l
Folate	7.4 μ g/l	1.6–6.0 μ g/l
Zinc	9.8 μ mol/l	8–17 μ mol/l
Copper	12.5 μ mol/l	13–27 μ mol/l
Magnesium	0.83 mmol/l	0.7–1.2 mmol/l
Total protein	52 g/l	60–80 g/l
Albumin	34 g/l	34–45 g/l
Calcium	2.13 mmol/l	2.26–2.0 mmol/l
Fasting triglyceride	0.3 mmol/l	0.8–2.0 mmol/l
Fasting cholesterol	1.2 mmol/l	2.5–8.8 mmol/l

Table 2 Serum levels of retinol in response to vitamin A therapy

	Retinol levels, $\mu\text{mol/l}$
Normal range	2.13–4.64
On admission	0.56
1 week	1.3
2 weeks	2.3
5 weeks	2.6
12 weeks	1.6
after admission and start of treatment	

tion his visual acuity had improved to R 6/18, L 6/12. His eyes were white and uninflamed, with an opaque but avascular right superior corneal graft, a similarly placed left corneal scar, and a small scar close to the left visual axis. He refuses to wear glasses to correct the right astigmatism (induced by the graft), though correction improves the visual acuity to 6/9. Fundus examination is almost impossible, as he develops intense blepharospasm on attempted ophthalmoscopy.

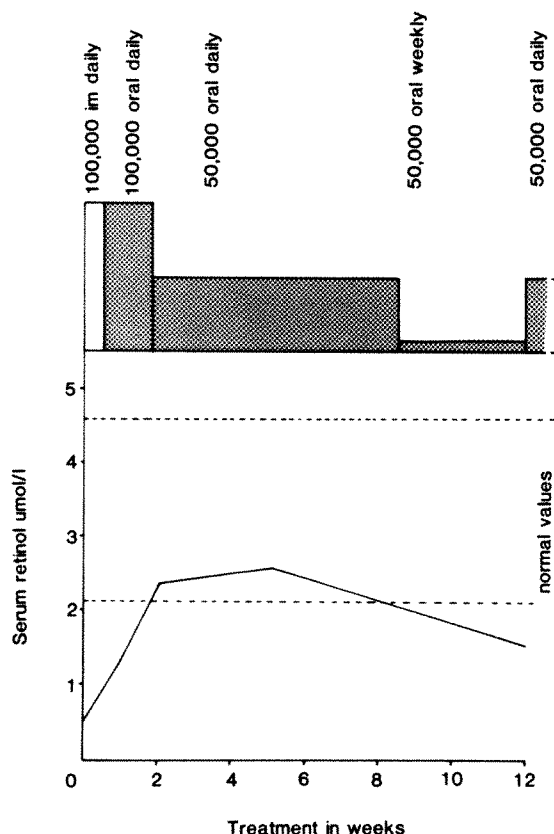


Fig. 2 Serum retinol levels in response to treatment.

Discussion

Vitamin A deficiency⁴ can cause nyctalopia, xerophthalmia, and keratomalacia. Night blindness was recognised in ancient Egyptian and Chinese writings in 1500 BC and was treated with liver, which is rich in vitamin A. It was also well known to the Greek and Roman physicians.

Keratomalacia is recorded in children in the industrial slums of nineteenth century Europe. By the early twentieth century it was rare, occurring only in isolated outbreaks such as the one in Denmark during the first world war.

Today vitamin A deficiency, xerophthalmia, and keratomalacia are rare in Western developed countries, but in many parts of the world keratomalacia is a major cause of blindness in children, particularly in Asia, certain parts of West Africa, the Middle East, Brazil, and Haiti. In these countries it is closely associated with protein malnutrition. A low dietary intake, compounded by hypoproteinaemia, results in a low level of retinol binding protein required to transport retinol in the plasma, while chronic intestinal infections and diarrhoea impair absorption of vitamin A and carotenoids.

Severe protein malnutrition is rare in the Western developed countries. Nyctalopia, the less severe form of vitamin A deficiency, occurs occasionally in malabsorption syndromes^{5,6} (short bowel syndromes in Crohn's disease and following resection for obesity) and severe liver disease,⁷ where it is often subclinical, detected only on dark adaptation testing^{8,9} or ERG.^{10,11} In the UK there is compulsory enrichment of margarine with vitamin A (approx. 800 IU/ounce=28 IU/g) and voluntary enrichment of skimmed milk powder. Therefore elderly people are unlikely to be at risk unless severely protein malnourished.

Keratomalacia has been reported¹² in an adult in the United States who had voluntarily eliminated all fresh fruit and vegetables from her diet in order to reduce exacerbations of her ulcerative colitis, and in a young man who deliberately eliminated all food containing vitamin A from his diet for five years in order to prevent his grand mal epilepsy.¹³ Both these patients were psychologically disturbed.

The patient reported on here was severely malnourished, as substantiated by biochemical investigation (Table 1). The ocular findings were consistent with keratomalacia and secondary bacterial infection. The yellow punctate retinopathy seen in the case of Bors and Fells¹³ was not observed, because even when the ocular media had cleared the patient developed acute blepharospasm on attempted fundal examination.

Particular problems were encountered in managing his chronic schizophrenia. It was difficult to obtain a clear history and to explain treatments, for he would embark on lengthy discussions, departing at tangents to the argument. He required a lengthy inpatient stay because he could not be relied on to continue his treatment or diet at home. In the investigation of this patient's ocular condition complicated tests were unhelpful. Dark adaptation tests or ERGs could not be performed as he would not co-operate. These tests might have been helpful in assessing progress if they had been possible, but in the circumstances his clinical course could be monitored only by external clinical examination and regular estimations of serum retinol levels. It seems likely, however, that most patients who develop vitamin A deficiency to this degree in Western countries are psychologically disturbed, so that the practicability of investigations requiring the patient's co-operation may be in doubt. Dark adaptation testing has been shown to be valuable in detecting subclinical deficiency of vitamin A in chronic alcoholism, primary hepatic disease, and chronic small intestinal disease. ERGs have a limited clinical use in detection only, as the abnormality of the a and b waves is of long duration even with a return to normal retinol levels, and therefore cannot be used as a therapeutic indicator.

Most Western ophthalmologists lack clinical familiarity with the ocular signs of vitamin A deficiency. They should be alert to a possible nutritional deficiency in a patient with unusual external ocular signs who may have a self induced nutritional deficiency, as in this case.

I thank Mr Peter Graham for allowing me to report this case. I am also grateful to Dr Max Harper, honorary consultant psychiatrist, and his colleagues for their advice with the psychiatric diagnosis and management of this patient.

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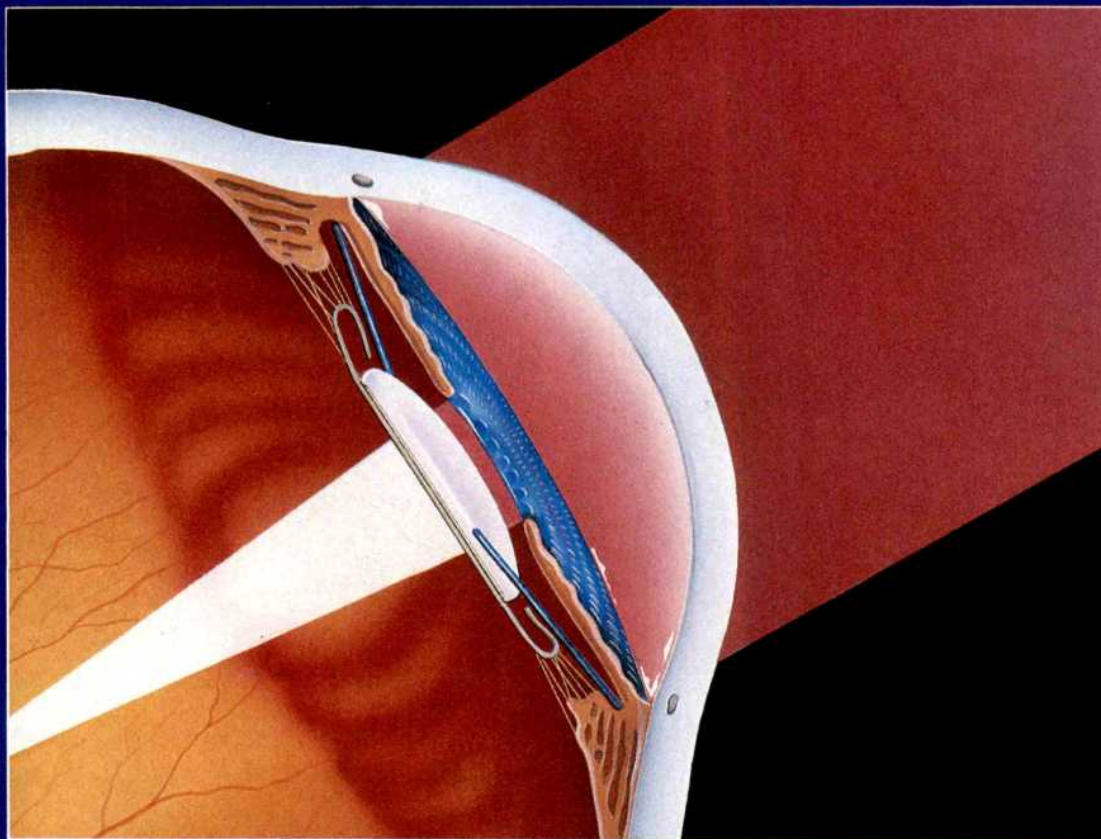


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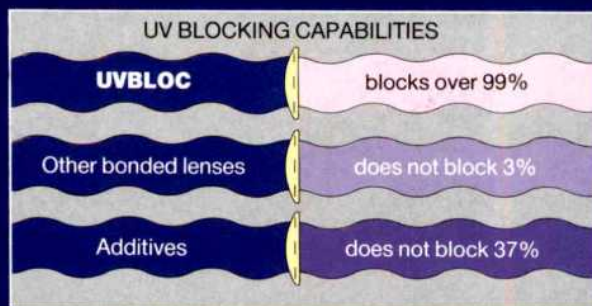
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Endocytosis in the retinal and choroidal microcirculation

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SUMMARY The endocytosis of horseradish peroxidase (HRP) by the vascular cells of retinal and choroidal blood vessels was compared in immersion and perfusion fixed eyes from individual rats. The mechanisms of endocytosis of HRP appeared identical in both retinal and choroidal vessels. The bulk of internalised tracer occurred in macropinosomes 300–400 nm in diameter. Tracer was localised to a 20–30 nm layer on the internal aspect of the limiting membrane. This layer was coincident with the glycocalyx of the luminal plasma membrane as revealed by ruthenium red-osmium tetroxide staining. Horseradish peroxidase was also internalised by a small scattered population of vesicles (100–130 nm in diameter). The size of these vesicles suggested that they may have arisen from clathrin coated regions of the plasma membrane. It is suggested that the endocytosis of HRP in retinal and choroidal vascular endothelium occurs as a function of plasma membrane recycling. Horseradish peroxidase may also be internalised as a 'contaminant' of the glycocalyx in coated pits involved in receptor mediated endocytosis. The smooth 80 nm plasmalemmal caveolae of the retinal and choroidal vascular endothelial cells did not appear to participate either in absorptive endocytosis or vesicular transport.

The retinal blood vessels are lined by a continuous non-fenestrated endothelium, the individual cells of which are joined by tight junctions. This layer of cells forms a highly selective barrier between the circulation and the extracellular space of the retinal neuro-pile, insulating the sensitive central nervous system neurones from the chemical milieu of the blood stream. The retinal vascular endothelium with its tight junctions has been termed the inner blood retinal barrier.¹

The permeability characteristics of the choroid are largely determined by the abundantly fenestrated choriocapillaris. Several ultrastructural studies have shown the choriocapillaris to be freely permeable to horseradish peroxidase^{2,3} and ferritin, though the basement membrane provides some impediment to the latter.⁴ The outer retina is separated from this highly permeable capillary network by the retinal pigment epithelial cells, which are linked by encircling tight junctions.

The eye therefore provides unique opportunities

for direct comparison of a 'barrier' circulation (retinal) with a highly permeable visceral type of circulation (choroidal) under identical experimental conditions. The fate of horseradish peroxidase was studied in the retinal and choroidal microvasculatures of individual animals after both immersion and perfusion fixation.

Materials and methods

All procedures on living animals were carried out under deep pentobarbital anaesthesia. Four rats were injected with horseradish peroxidase (Sigma Type VI, 20 mg/100 g body weight in normal saline via the femoral vein), which was allowed to circulate for 15 minutes before enucleation of the left eye and perfusion fixation of the right. The distribution of peroxidase reaction product was compared in immersion and perfusion fixed retina and the adherent choroid of the same tissue slices. As controls two non-injected siblings were fixed by vascular perfusion and slices of retina and choroid incubated for endogenous peroxidase activity.

Immersion fixation of tissues under study was

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carried out in 2.5% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4) containing 0.025% magnesium chloride for three hours. Perfusion fixation was accomplished via the ascending aorta with a simple gravity-feed apparatus. A 6-foot (180 cm), head of fluid has been recommended for perfusion fixation of neural tissues in rats, cats, and monkeys.⁵ However, the resultant intravascular pressure in the eye produced some tearing of the intima in the choroidal arteries. A pressure head of 4 feet (120 cm) was found to give equally good fixation free of discernible artefact. A 2.5% solution of glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) was used for perfusion fixation. A 10-second prewash of phosphate buffered saline was given prior to infusion with fixative. Perfusion fixation was continued for 30 minutes in situ followed by a 2-hour immersion in fixative (above). Post-fixation was carried out in 1% osmium tetroxide for 2 hours at 4°C. For cytochemical demonstration of horseradish peroxidase 100 µm tissue-chopped sections were presoaked for 3 hours at 4°C in a mixture containing 10 mg diaminobenzidine tetrahydrochloride (DAB) in a 0.1 M cacodylate buffer pH 7.4 followed by a 3-hour incubation at room temperature in the same solution at pH 5.1 (pH optimum of horseradish peroxidase)* with the addition of 0.1 ml of 1% hydrogen peroxide per 10 ml. Osmication was as described above.

To demonstrate the luminal cell coat or glycocalyx of the retinal vascular endothelium the eyes of four additional rats were fixed by vascular perfusion with 2.5% glutaraldehyde in a 0.1 M cacodylate buffer (pH 7.2) containing 0.5% ruthenium red. Fixation

was continued for 15 minutes in situ followed by immersion for a further 45 minutes in the same fixative. The retinæ were dissected and small tissue blocks cut into thin slices. All tissue slices were given three 10-minute washes in 0.1M cacodylate buffer containing 0.5% ruthenium red prior to staining in ruthenium red/osmium tetroxide after the method of Luft.⁷

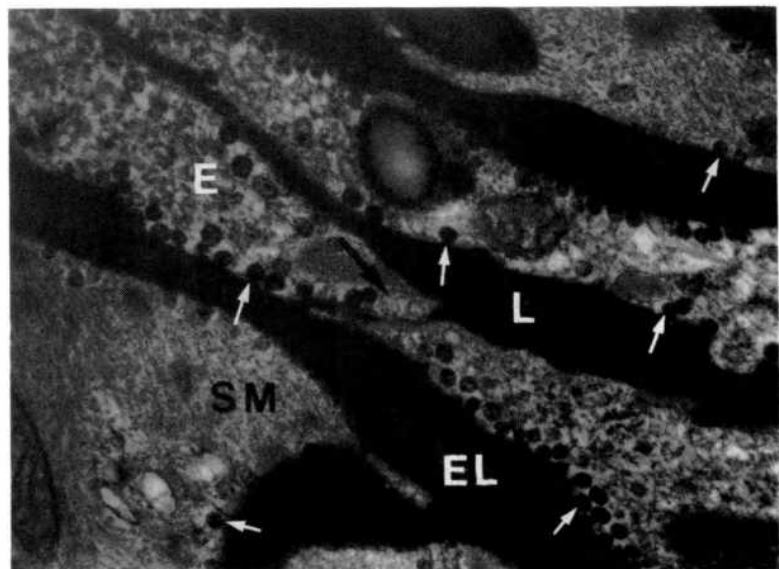
All tissue samples were dehydrated with ethanol and embedded in TAAB resin. Thin sections were cut on a Reichert OMU4 ultramicrotome, stained with lead citrate, and photographed on either an AEI Corinth 500 or Philips 301 electron microscope.

Results

ENDOCYTOSIS OF HORSERADISH PEROXIDASE BY THE VASCULAR CELLS OF THE CHOROID

Electron micrographs of immersion fixed specimens showed that after 15 minutes' exposure to horseradish peroxidase the protein had filled the entire extravascular space of the choroid, outlining cell bodies and connective tissue fibres as negative images within the blackened extracellular matrix. In the choroidal arteries the tracer had outlined large arrays of 80 nm plasmalemmal caveolae on both the luminal and abluminal plasma membranes of the endothelial cells (Fig. 1). Closely associated with the caveolae were many presumptive micropinocytotic vesicles showing apparent internalisation of peroxidase (Fig. 1). The endothelial cells in these vessels were joined by occluding junctions which proved 'tight' to peroxidase (Fig. 1). Plasmalemmal caveolae and

Fig. 1 Choroidal artery (rat): immersion fixation. Horseradish peroxidase reaction product fills the plasmalemmal caveolae (white arrows) and associated vesicles of the luminal and abluminal plasma membranes of the endothelial cells (E) and the sarcolemmal caveolae (white arrows) of the smooth muscle cells (SM). The intercellular clefts of the endothelium and caveolae of the lateral plasma membranes (black arrow) remain free of peroxidase reaction product. Lumen (L), internal elastic lamina (EL). ($\times 25\,000$).



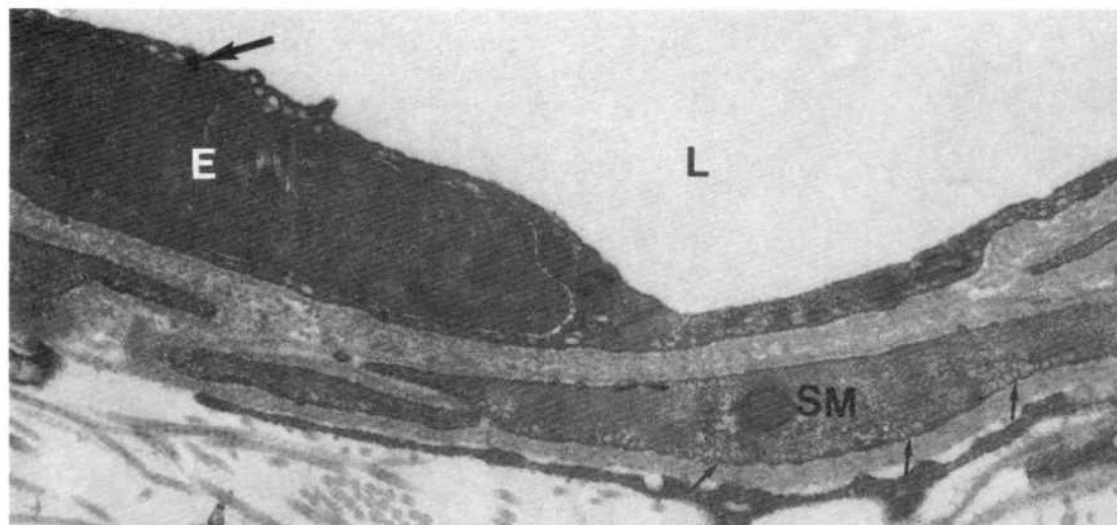


Fig. 2 Choroidal artery (rat): perfusion fixation. The plasmalemmal caveolae and vesicles of the endothelium (E) are largely free of peroxidase. Only a solitary luminal vesicle shows true internalisation (large arrow). The sarcolemmal caveolae of the adjacent smooth muscle cells (SM) are empty (small arrows) and the cells show no evidence of endocytosis. Lumen (L). ($\times 16\,000$).

associated vesicles of the lateral plasma membranes lying within the 'protected' intercellular clefts (bounded by tight junctions) remained free of peroxidase (Fig. 1). The sarcolemmal caveolae of the arterial smooth muscle cells stained uniformly with peroxidase. The plasmalemmal caveolae and associated vesicles in the endothelial cells of the choroidal veins and capillaries also stained consistently with peroxidase.

Perfusion fixed choroid bore little resemblance to the immersion fixed material already described. Although the prewash was brief (10 seconds) it was sufficient to purge the extracellular space of peroxidase. The endothelial cells of the arteries still

displayed large numbers of plasmalemmal caveolae and vesicles; however, the vast majority of these were now empty (Fig. 2). Truly internalised enzyme was present in only a small scattered population of vesicles (100–130 nm), some large endocytic vacuoles (300–400 nm), multivesicular bodies, and dense, presumably heterophagic, vacuoles. (Peroxidase labelled endocytic vacuoles and multivesicular bodies were more common in choroidal veins and venules and will be illustrated in relation to those vessels.)

Peroxidase labelled endocytic vacuoles were more common in the choroidal veins and venules than in the arteries. Much of the endocytic activity in these

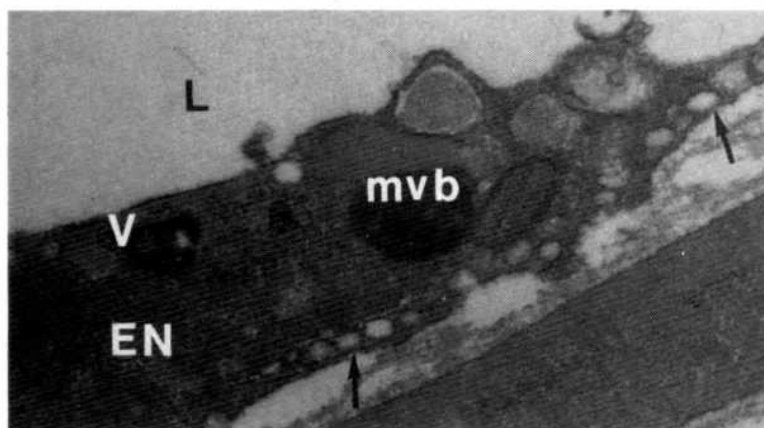


Fig. 3 Choroidal vein (rat): perfusion fixation. Endothelial cell shows peroxidase reaction product within an endocytic vacuole (V) and a multivesicular body (mvb). Note stomatal diaphragms of plasmalemmal caveolae (arrows). Endothelial cell nucleus (EN). ($\times 45\,000$).

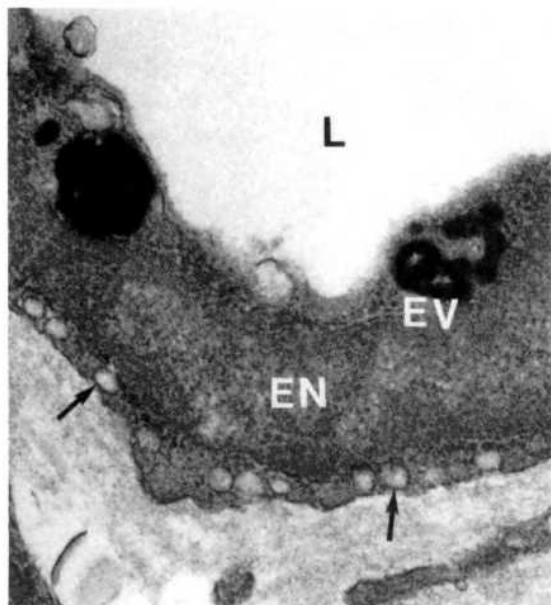


Fig. 4 Choroidal vein (rat): perfusion fixation. Peroxidase reaction product in endocytic vacuoles and dense bodies of venous endothelial cell. One profile suggests collapse and folding of the original vacuole (EV). Note stomatal diaphragms of plasmalemmal caveolae (arrows). Endothelial nucleus (EN), lumen (L). ($\times 45\,000$).

vessels occurred in the perinuclear cytoplasm (Fig. 3). Some profiles of endocytic vacuoles suggested collapse and folding of the limiting membrane (Fig. 4).

All the elements of the endocytic system described in the choroidal arteries and veins could be identified in the non-fenestrated regions of the choriocapillary

endothelial cells. However, the highly attenuated 'stretched out' nature of these cells made peroxidase labelled bodies seem sparse when compared with the more bulbous endothelium of the arteries and veins.

Peroxidase reaction product in the endocytic vacuoles was usually localised to a regular layer 20–30 nm thick on the inner surface of the limiting membrane, leaving an electron transparent core (Fig. 5). Although it was impossible to observe macropinocytosis in this model (perfusion fixation removes incompletely internalised tracer), the pseudopodia associated with the phenomenon were often seen at the luminal plasma membrane (Fig. 5).

The clarification of the extracellular space by perfusion fixation permitted a better evaluation of the plasmalemmal caveolae of the endothelium and those of the neighbouring smooth muscle cells. A large population of the caveolae had their stomata closed by thin flocculent diaphragms. Caveolae without diaphragms were usually located on the luminal plasmalemma. Diaphragms also covered the caveolae of the smooth muscle cells of the arteries and the pericytes of the veins and capillaries. All such caveolae were free of peroxidase following perfusion fixation (Fig. 6). Despite the vast arrays of caveolae present along the plasma membranes of the smooth muscle and pericyte cells no internalised tracer was detected in their cytoplasm.

Peroxidase was also taken up by many choroidal fibroblasts and occasional wandering macrophages. The endocytic vacuoles in both these cell types were almost identical to those encountered in the vascular endothelium, having an electron transparent core and 20–30 nm layer of peroxidase stained material on the internal aspect of the limiting membrane.

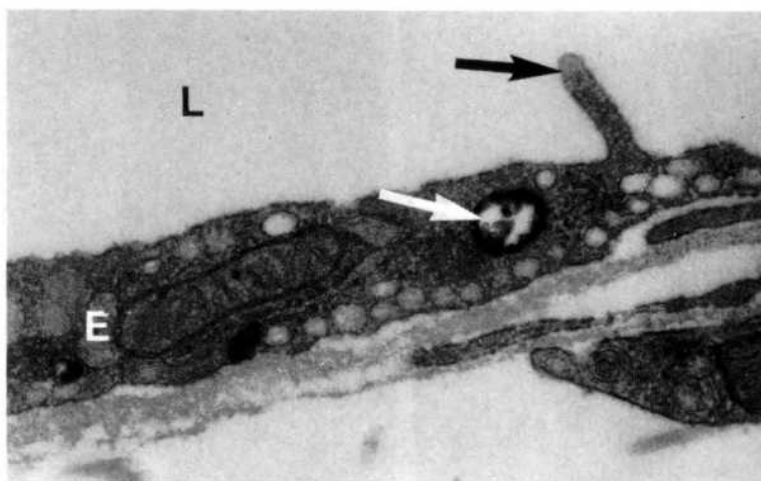


Fig. 5 Choroidal vein (rat): perfusion fixation. Peroxidase reaction product within endocytic vacuole of endothelial cell (E) is localised to a 20–30 nm layer on the inner surface of the limiting membrane (white arrow). Lumen (L), pseudopodia (black arrow). ($\times 45\,000$).

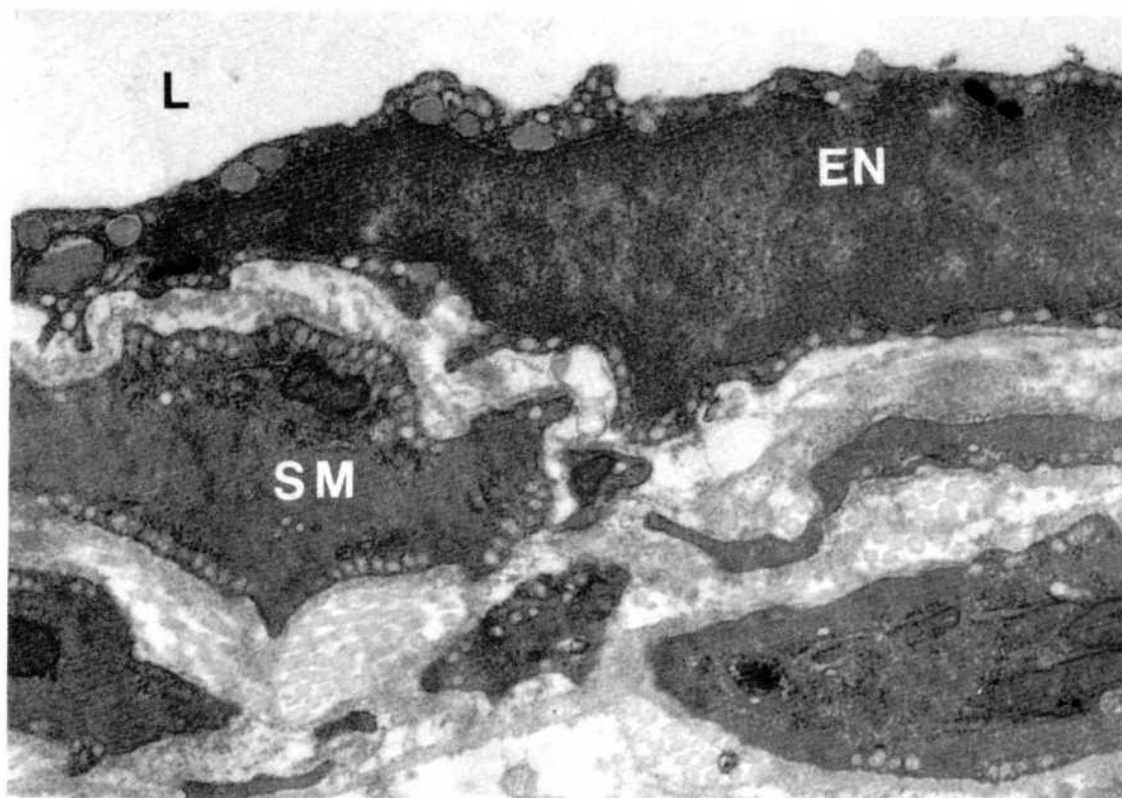


Fig. 6 Large choroidal vein (rat): perfusion fixation. The plasmalemmal caveolae of the endothelium and sarcolemmal caveolae of the smooth muscle cells (SM) are free of peroxidase after perfusion fixation. Endothelial nucleus (EN). ($\times 23\,730$).

ENDOCYTOSIS OF HORSE RADISH PEROXIDASE BY THE VASCULAR CELLS OF THE RETINA

The endocytosis of circulating peroxidase by vascular endothelial cells in the retina is somewhat different from the choroid in that (because of the blood retinal barrier) only the luminal plasma membrane is exposed to the tracer. Immersion fixed specimens of retinal blood vessels exposed to intravascular peroxidase for 15 min revealed peroxidase reaction product throughout the fixed intraluminal plasma proteins (Fig. 7). There was also uniform staining of a 20–30 nm thick layer on the luminal surface of the endothelial cells. This layer covered the entire luminal surface, including the inside of the plasmalemmal caveolae and associated 'vesicles' (Fig. 7). An identical layer of peroxidase reaction product lined the internal surfaces of endocytic vacuoles (300–400 nm diameter) (Fig. 7) and vesicles (100–130 nm diameter) (Fig. 8), leaving electron transparent core regions. On several occasions a similar layer (20–30 nm) of peroxidase reaction product was found within cisternae of the Golgi apparatus (Fig. 9). However, in such instances staining was

confined to the trans end of the stack. Peroxidase was also found in large lysosome-like structures and in multivesicular bodies which were generally labelled after 15 minutes exposure to the tracer. In multivesicular bodies where good localisation had been achieved the enclosed vesicles were seen to be free of peroxidase, which was confined to the matrix of the body (Fig. 10).

Perfusion fixed specimens showed no adsorbed peroxidase at the luminal plasmalemma of the retinal endothelial cells (Fig. 11). Furthermore, only a tiny proportion of the apparently labelled 'vesicles' observed in immersion fixed specimens were found to be truly internalised. The bulk of internalised tracer was found to reside in the large endocytic vacuoles described above. All the vessels examined in this study showed an overwhelming preponderance of plasmalemmal caveolae at the abluminal cell surface as compared to the luminal plasmalemma (Fig. 11).

RUTHENIUM RED STAINING OF THE LUMINAL CELL COAT OF THE RETINAL ENDOTHELIUM
Ruthenium red/glutaraldehyde primary fixation and

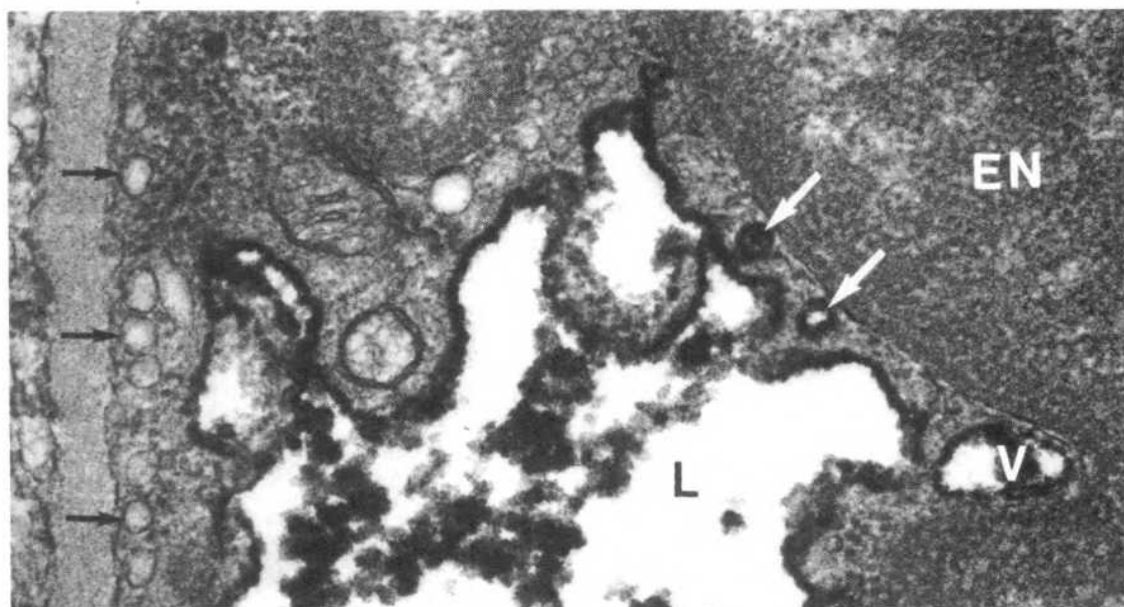


Fig. 7 Retinal capillary (rat): immersion fixation. Peroxidase reaction product stains a 20–30 nm layer on the luminal cell surface. A similar layer coats the inside of an endocytic vacuole (V) and adjacent 'vesicles' (white arrows). Lumen (L), endothelial cell nucleus (EN). Note abluminal plasmalemmal caveolae (black arrows). ($\times 56\,450$).

ruthenium red/osmium tetroxide staining produced a highly electron opaque product within the luminal surface coat of the retinal endothelial cells. The cell surface was completely invested by this coat, which was in intimate contact with the outer leaflet of the plasma membrane. The stained layer, which was 20–30 nm deep, lined the inside of the plasmalemmal caveolae (Fig. 12) and adjacent 'vesicles' (Fig. 13), leaving an electron transparent core region. However, in all instances where 'vesicle' images were encountered in these preparations the adjacent plasma membrane was obviously in oblique section (Fig. 13).

Discussion

CHOROID

The endothelial fenestrations of the choriocapillaris afford a small protein such as horseradish peroxidase (MW 43 000, Einstein-Stokes radius 3 nm)⁸ unlimited access to the extracellular space of the choroid, thus presenting the protein to both luminal and abluminal aspects of the endothelium within a short period of time. In the choroidal arteries this effect served to demonstrate the presence of tight junctions between the endothelial cells and to outline 'privileged areas' of the intercellular clefts bounded by them. Examination of these privileged zones revealed plasmalemmal caveolae on the lateral plasma membrane which also

remained free of peroxidase. Such caveolae have been associated with macromolecular transport^{9,10} yet occur on surfaces from which circulating proteins at least as large as horseradish peroxidase are excluded.

Another consequence of simultaneously filling the vascular lumen and extracellular space with tracer was that almost every pit and vesicle on the luminal and abluminal plasma membranes appeared labelled, together with the sarcolemmal caveolae of the smooth muscle cells and pericytes. This picture would have proved misleading had identical perfusion fixed choroid not been available. Following a short buffer 'washout' of the extracellular space and perfusion fixation the great majority of the labelled endothelial 'vesicles' had to be reconsidered as plasmalemmal caveolae whose stomata lay outside the plane of section.

The change in the caveolae of the smooth muscle cells was even more dramatic after perfusion fixation, all pits and vesicles being completely empty, with no genuinely internalised peroxidase. This finding was predictable, as Gabella¹¹ has shown that, in smooth muscle cells, caveolae have a role in surface area modulation but not in endocytosis. In smooth muscle cells it is likely that caveolae facilitate the transport of calcium ions across the sarcolemma.^{12,13}

The caveolae of the smooth muscle cells were indistinguishable from those of the endothelium, many examples of each having their stomata covered

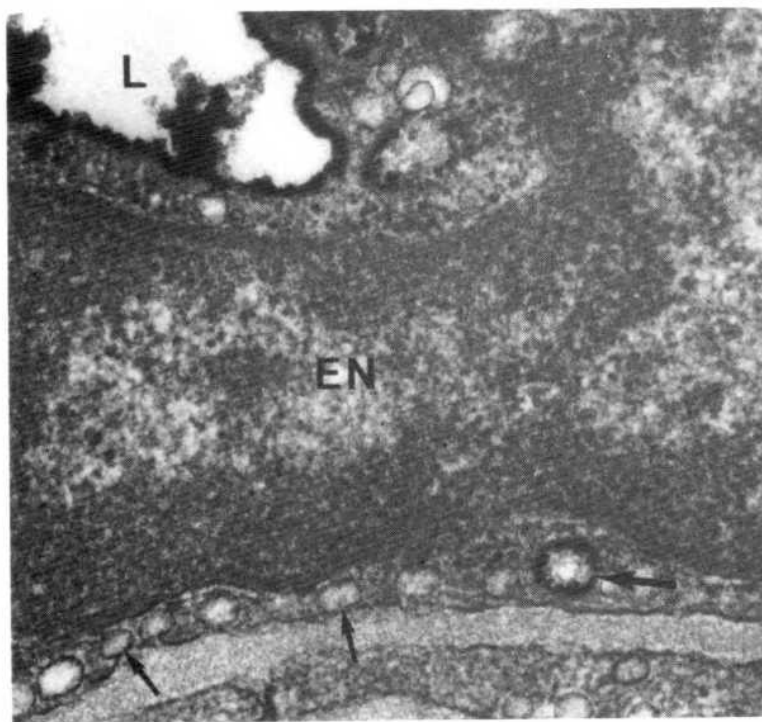


Fig. 8 Retinal capillary (rat): immersion fixation. Peroxidase reaction product coats luminal cell surface and a 20–30 nm layer on the internal surface of an endocytic vesicle at the abluminal plasmalemma. Note the endocytic vesicle (large arrow) is considerably larger than the plasmalemmal caveolae adjacent to it (small arrows). Endothelial cell nucleus (EN), lumen (L). ($\times 60\,000$).

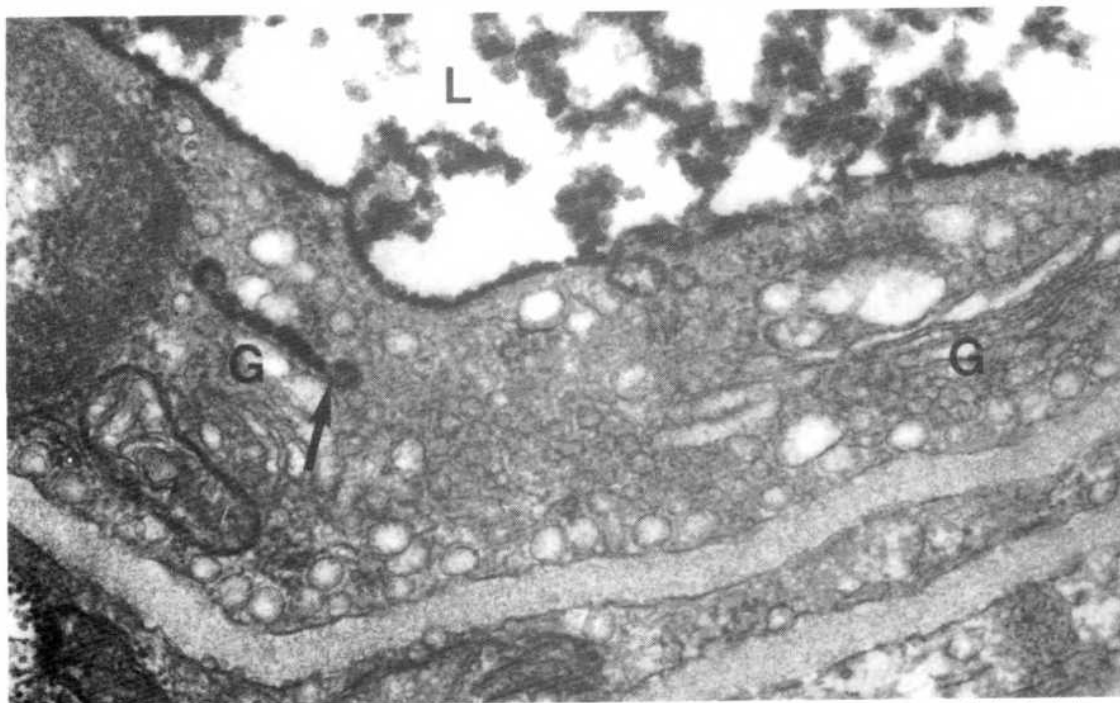
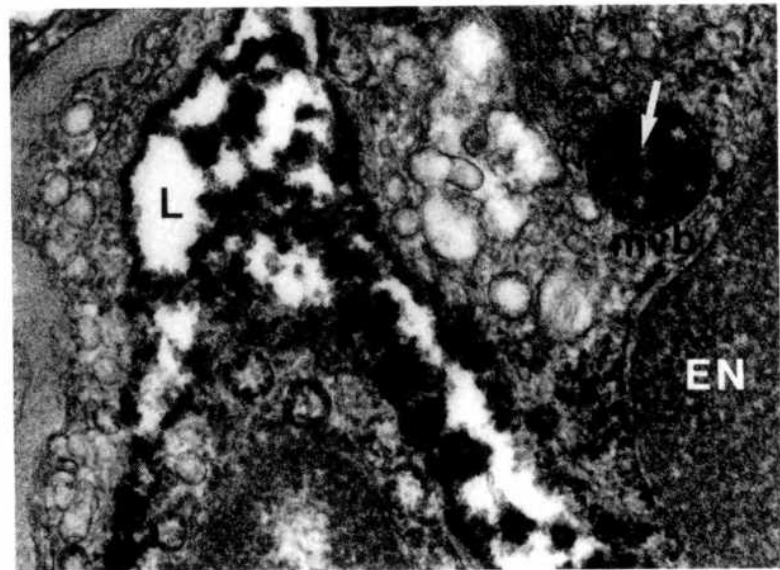


Fig. 9 Retinal capillary (rat): immersion fixation. Peroxidase reaction product stains a 20–30 nm layer on the luminal plasma membrane of the endothelial cell and a similar layer on the internal aspect of a trans Golgi saccule (arrow). Golgi apparatus (G), lumen (L). ($\times 58\,300$).

Fig. 10 Retinal capillary (rat): immersion fixation. Peroxidase reaction product is present in the matrix of a multivesicular body (mvb) but not in the enclosed vesicles (arrow). Endothelial cell nucleus (EN), lumen (L). ($\times 60\,000$).



by a diaphragm. As caveolae without diaphragms usually occurred on the luminal plasma membranes of the endothelial cells, it was thought that the diaphragms had been lost during perfusion fixation. While the diaphragms covered the caveolae, they clearly did not close them to molecules at least as large as those of horseradish peroxidase. Smooth-coated 80 nm plasmalemmal caveolae closed by diaphragms were first described by Bruns and Palade^{14,15} in muscle capillaries, where they were thought to be involved in vesicular transport. Tracer studies by Bruns and Palade¹⁵ and Simionescu *et al.*^{9,10} suggested that the plasmalemmal caveolae gave rise to micropinocytotic vesicles which operated a trans-endothelial vesicular shuttle ferrying macromolecules from one side of the vascular endothelium to the other. If the extensive arrays of plasmalemmal caveolae seen on both luminal and abluminal endothelial cell membranes in the larger choroidal vessels derive from or give rise to transport vesicles, it must be assumed that the transcellular passage of the vesicles is extremely rapid, as 'in transit' examples were rare. It could be argued that the few labelled vesicles which were seen in a mid-way position could have arisen from clathrin-coated crypts¹⁶ and were bound for an intracellular destination as judged by the numerous labelled multivesicular bodies and presumptive heterophagic vacuoles. Furthermore, considering the efficiency of the nearby choriocapillary bed (extracellular space purged of peroxidase in less than 10 seconds) and the high exclusion limit of its endothelial fenestrations (pass ferritin MW 480 000 E-S radius 6 nm)⁸ the transcellular transport of macromolecules seems superfluous.

The concept of vesicular transport in vascular endothelia has recently been seriously challenged by Frøkjaer-Jensen¹⁷ and Bundgaard *et al.*^{18,19} who, in studies of 14–15 nm serial sections, concluded that the plasmalemmal vesicles of vascular endothelia are units of an extensive system of racemose invaginations of the plasmalemma and are seldom if ever found free in the cytoplasm. These findings prompted Crone²⁰ to suggest that the use of the term 'micropinocytosis' be discontinued. Therefore it seems likely that the plasmalemmal caveolae of vascular endothelial cells may have an analogous role to those in smooth muscle cells. The expansion of the cell surface provided by such structures would provide more usable membrane for discrete functions such as simple or facilitated diffusion or active transport. Such a role for endothelial caveolae is supported by studies indicating the presence of enzymes associated with active transport within them.²¹

The endocytosis of horseradish peroxidase in the choroidal endothelia, whether in small vesicles or large vacuoles, appeared to be a function of plasma membrane recycling. Tracer was invariably internalised after adsorption to a 20–30 nm thick layer on the external surface of the luminal plasma membrane. This layer, which was thought to represent the luminal cell coat or glycocalyx of the endothelium,²² persisted until the form of the original vacuoles was lost following fusion with multivesicular bodies or lysosomes.

RETINA

The peroxidase labelling characteristics of the retinal

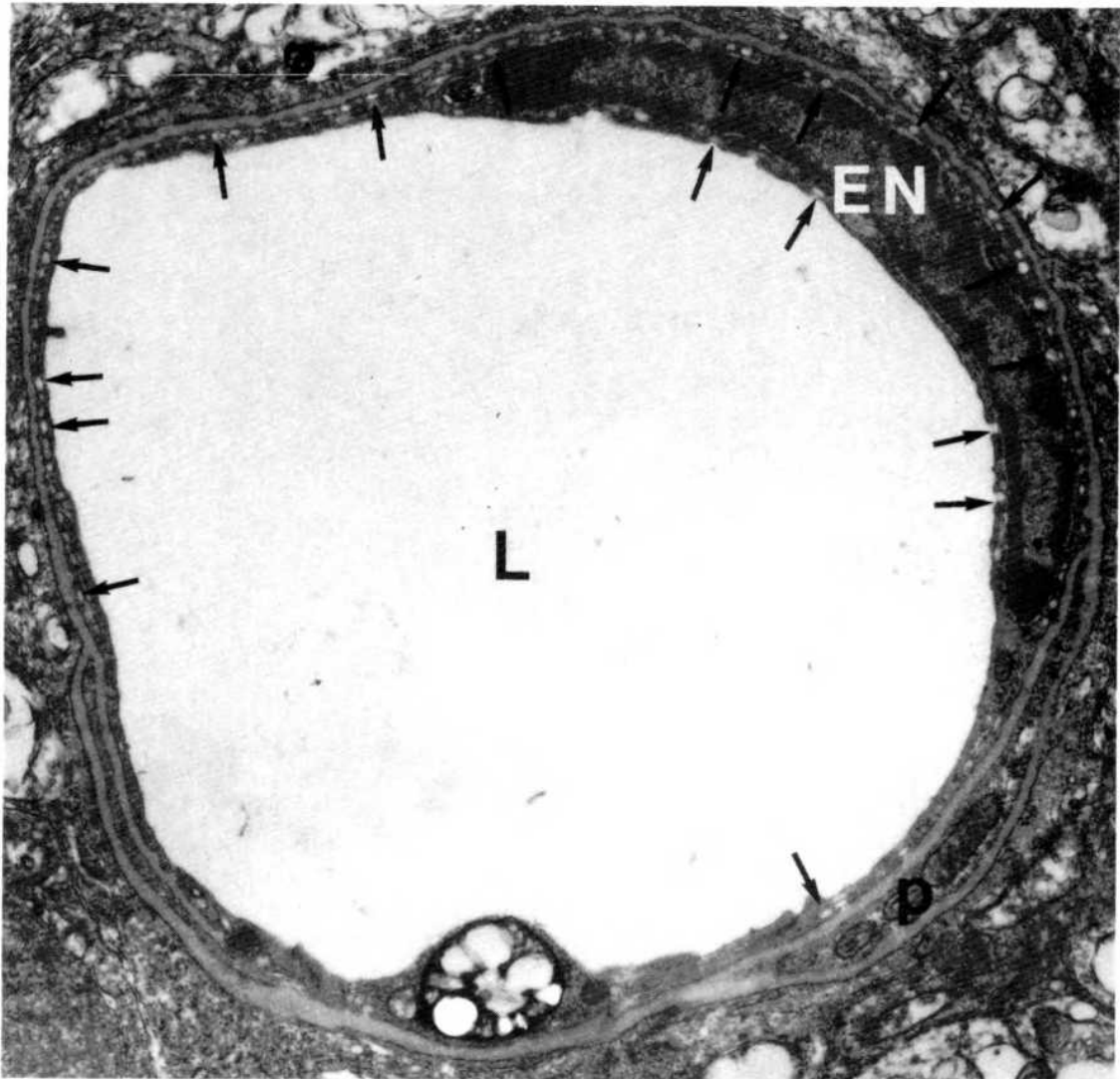
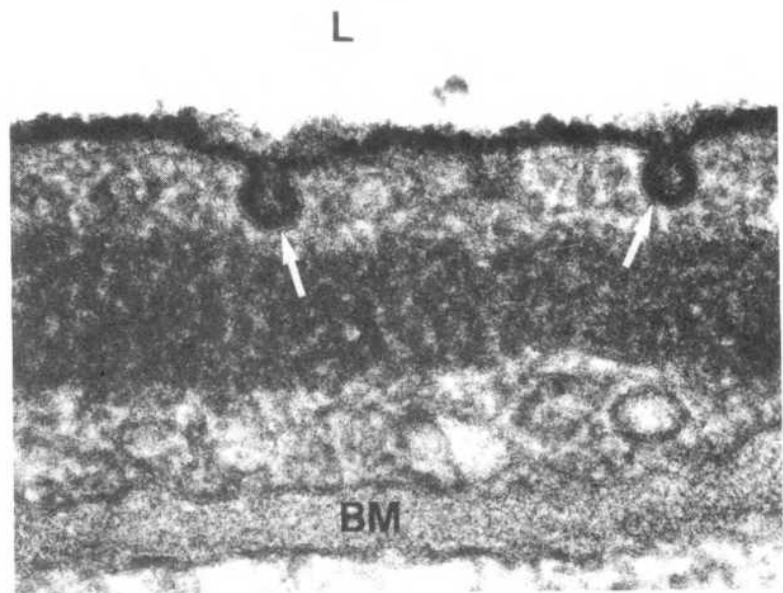


Fig. 11 Retinal venule (rat): perfusion fixation. Peroxidase reaction product stains a large lysosome-like inclusion. The plasmalemmal caveolae and associated vesicles appear empty (arrows). Note preponderance of abluminal over luminal caveolae. Endothelial cell nucleus (EN), lumen (L), pericyte process (P). ($\times 19\,100$).

vascular endothelium differed only quantitatively from the choroidal vessels, showing a similar distribution between small vesicles and large vacuoles. The large endocytic vacuoles were thought to arise through simple folding and fusion of the luminal plasmalemma and to represent a recycling phenomenon of the plasma membrane. The few unambiguously labelled vesicles which were found free in the cytoplasm were of an order of magnitude (100–130 nm) which excluded them as derivatives of the 80 nm diameter plasmalemmal caveolae but suggested that they may have arisen from clathrin coated pits.

A 20–30 nm layer of peroxidase stained material covered the entire luminal surface of immersion fixed retinal endothelial cells and lined the interior of the endocytic vacuoles. This layer was assumed to be the peroxidase stained cell coat or glycocalyx of the luminal plasma membrane and was identical to that of choroidal endothelial cells. The bulk of internalised plasma membrane and its peroxidase labelled coat material was incorporated into either heterophagic vacuoles or multivesicular bodies. The multivesicular bodies or endosomes²³ probably became labelled through incorporation of vesicles derived

Fig. 12 Retinal venular endothelial cell (rat): perfusion fixation plus ruthenium red/osmium tetroxide staining. Positive staining is confined to a 20–30 nm layer on the outer surface of the luminal plasmalemma. The stained layer is in close apposition to the outer leaflet of the membrane and coats the inside of the plasmalemmal caveolae (arrows). Lumen (L), basement membrane (BM). ($\times 110\,000$).



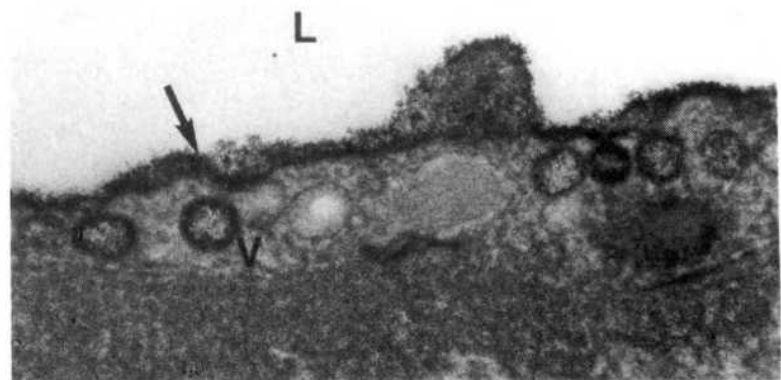
from clathrin coated areas of the plasma membrane. Clathrin coated crypts are common in retinal vascular endothelial cells, and, although they are known to be involved in receptor mediated endocytosis,²³ their glycocalyx may be stained non-specifically by adsorbed cationic peroxidase.

The mechanism of endocytosis in retinal and choroidal vessels appeared identical. Peroxidase remained bound to the glycocalyx of the plasmalemma until the form of the original endocytic vesicle or vacuole was lost during fusion with multivesicular bodies or lysosomes. Although the binding of peroxidase to the glycocalyx was weak (it washes off in prewash of perfusion fixation), it was found to persist

following fusion of recycled plasma membrane with trans-Golgi cisternae. This phenomenon has not been previously illustrated in vascular endothelial cells but is in accord with plasma membrane retrieval studies on several different cell types.^{24–27} In these studies tracer labelled membrane from the cell surface appeared exclusively at the trans end of the Golgi stack.

This study confirms that the endocytosis of horseradish peroxidase occurs by virtue of its association with the glycocalyx of recycled plasma membrane. Most commercial horseradish peroxidase contains several cationic isoenzymes and as such may show some non-specific binding to the anionic surface coat

Fig. 13 Retinal venular endothelial cell (rat): perfusion fixation plus ruthenium red/osmium tetroxide staining. Positive staining is present in the surface coat of the luminal plasma membrane and the internal aspect of the plasmalemmal caveolae. An apparent 'vesicle' (V) shows positive staining, but the adjacent plasma membrane is obviously in oblique section (arrow). Lumen (L). ($\times 80\,000$).



or glycocalyx present around most cells.²² This coat is rich in polyanions, which give it a net negative charge and render it stainable with cationic dyes such as ruthenium red. The glycocalyx is indistinct in conventional electron microscopic preparations, though it may be demonstrated indirectly by adsorption of a demonstrable substrate, such as horseradish peroxidase.²³ In the present context horseradish peroxidase may be described as a general marker of endocytosis, for, although it is itself internalised by a non-concentrative process, if present in the extracellular medium it may be non-specifically adsorbed to the glycocalyx covering clathrin coated pits²⁴ involved in highly concentrative receptor mediated endocytosis.²⁵

A luxuriant glycocalyx has been demonstrated on the luminal surface of vascular endothelial cells in other tissues.^{26,27} That the 20–30 nm peroxidase adsorption zone observed in the present study was coincident with the luminal surface coat of the retinal endothelium was confirmed by direct staining with ruthenium red. The regular 20–30 nm thick layer revealed by ruthenium red on the luminal surface of the retinal endothelium proved identical both in thickness and distribution to the peroxidase adsorption zone observed above. As the same layer of stained material seen on the plasmalemma proper was found to coat the caveolae, oblique sections through such caveolae produced images identical to the peroxidase labelled vesicles described above—that is, a 20–30 nm electron opaque layer tightly apposed to the limiting membrane, leaving an electron transparent core region.

As macropinocytosis is common at the luminal plasma membrane of retinal and choroidal vascular endothelial cells, it seems likely that this system corresponds to the major pathway for plasma membrane recycling in such cells and that the uptake of extracellular protein by the system is fortuitous. As electron micrographs of these vacuoles show that demonstrable tracers are confined to a thin layer on the internal surface of the limiting membrane while the rest of the vacuole appears artificially empty, it is proposed that macropinocytosis occurs through simple folding and fusion of plasma membrane without any significant attempt to imbibe fluid from the extracellular medium. Furthermore, in comparison with receptor mediated endocytosis²³ the uptake of extracellular fluid, with its low concentration of nutrient and contamination by metabolic wastes, seems inefficient, especially when coupled to the gross membrane recycling entailed in the process. The endocytosis of horseradish peroxidase, by virtue of its association with the cell coat or glycocalyx, defines it as a general marker of plasma membrane retrieval rather than an indicator of fluid uptake.

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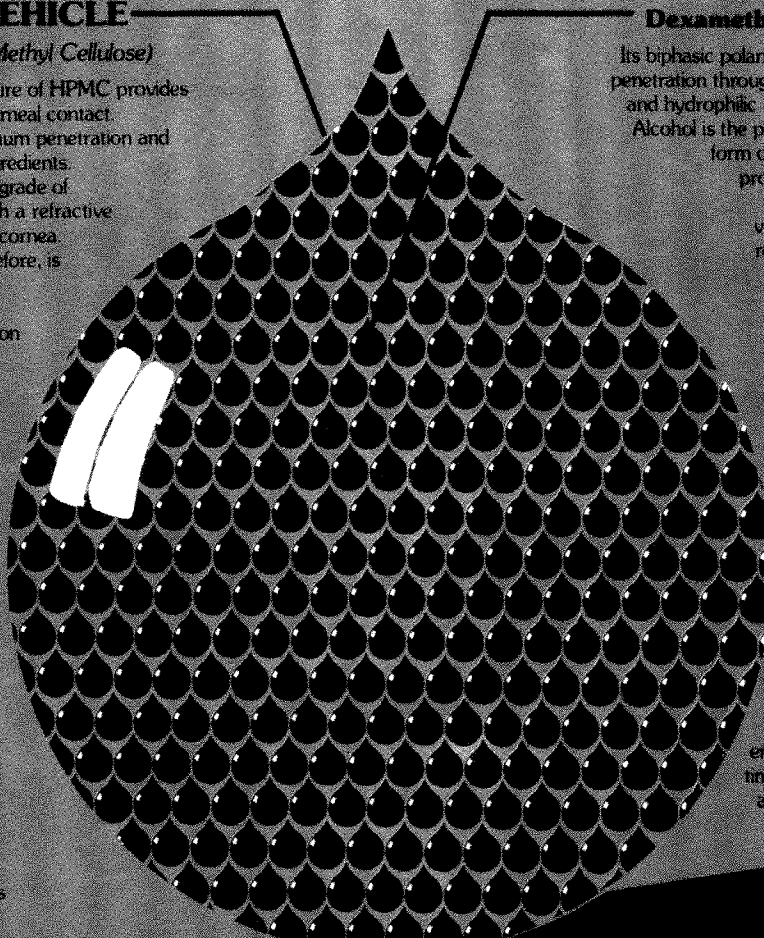
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Ocular toxicity of desferrioxamine: light microscopic histochemical and ultrastructural findings

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SUMMARY This study documents for the first time light and electron microscopical changes in the retinal pigment epithelium (RPE) following treatment with high dose desferrioxamine for systemic iron overload. The changes include loss of microvilli from the apical surface, patchy depigmentation, vacuolation of the cytoplasm, swelling and calcification of mitochondria, and disorganisation of the plasma membrane. In addition, Bruch's membrane overlying degenerate RPE cells appeared abnormally thickened owing to the accumulation of large amounts of mature elastic fibres, pre-elastic oxytalan, and long spacing collagen. The specificity of these changes and the mechanism of toxicity are discussed.

Desferrioxamine (diethylenetriamine penta-acetic acid), an iron chelating agent, is extensively used for the treatment of systemic iron overload, ocular siderosis, and corneal rust staining. It was first isolated in 1960¹ from sideramine, an iron-containing metabolite of actinomyces. Ocular toxicity of desferrioxamine came to light only recently when four patients with β -thalassaemia major were treated with a high intravenous dose to counter the effects of transfusion-induced iron overload.² Two patients developed night blindness and field defects which were improved on withdrawal of the drug. Recently one of the two affected patients died from heart

failure, and we were able to obtain an eye to study the structural lesions of ocular toxicity. We report here the relevant histochemical, light microscopic, scanning, and transmission electron microscopic findings.

Material and methods

The deceased was a 24-year-old male who had received regular blood transfusion from the age of 6 months for the treatment of β -thalassaemia major. He underwent splenectomy at the age of 16 years. To prevent iron overload and subsequent damage to the liver and other organs he received intramuscular desferrioxamine 500 mg daily from age 8 years. From age 19 he received his desferrioxamine by overnight subcutaneous infusion.

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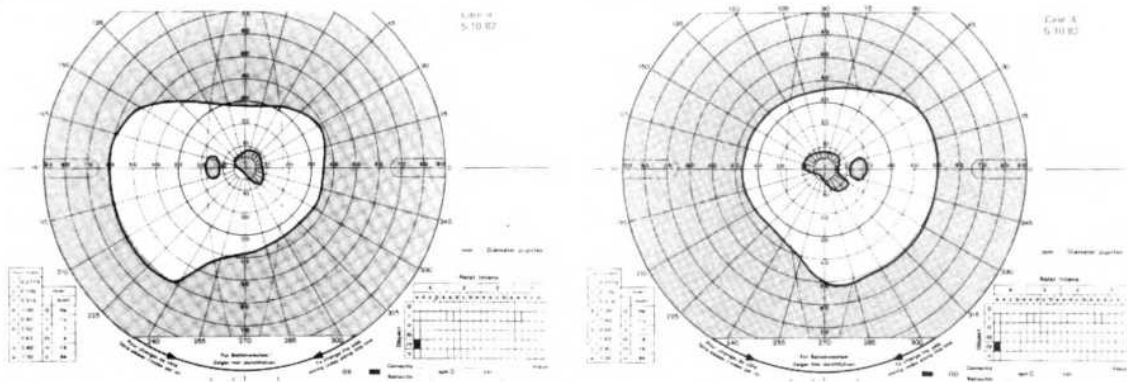


Fig. 1 Visual fields during high-dose desferrioxamine therapy.

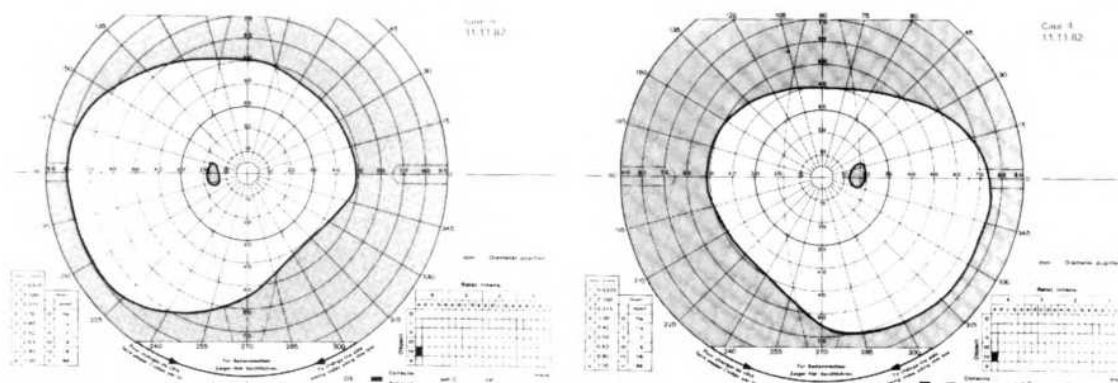


Fig. 2 Visual fields after withdrawal of high-dose desferrioxamine therapy.

In 1982 he was admitted as an emergency and was treated for congestive cardiac failure at University College Hospital, London. His serum ferritin was very high (11 000 $\mu\text{g/l}$) and intravenous desferrioxamine was started, 165 mg/kg per 24 h for two days, then 220 mg/kg per 24 h for six days. Eight days after the start of intravenous therapy he complained of poor vision in dim light. The treatment was stopped. Detailed ophthalmological examination showed bilateral reduced visual acuity (6/36) and impaired

colour vision. Visual field examination revealed a small central scotoma in each eye and generalised constriction of the peripheral field (Fig. 1). Within what field remained, scotopic static perimetry showed a reduction in dark adaptation greatest in the central and equatorial zones. There were no lens opacities or obvious pigmentary disturbance in the retina, but the retinal vessels were thin and tortuous. The electro-oculogram (EOG) was severely reduced and the Ganzfeld electroretinogram (ERG) was

Fig. 3 Paraffin section of the eye showing iron-containing stromal cells in the choroid. Note that occasional retinal pigment epithelial cells are enlarged and appear to project towards the photoreceptors, which appear normal. (Perls's stain, $\times 250$).

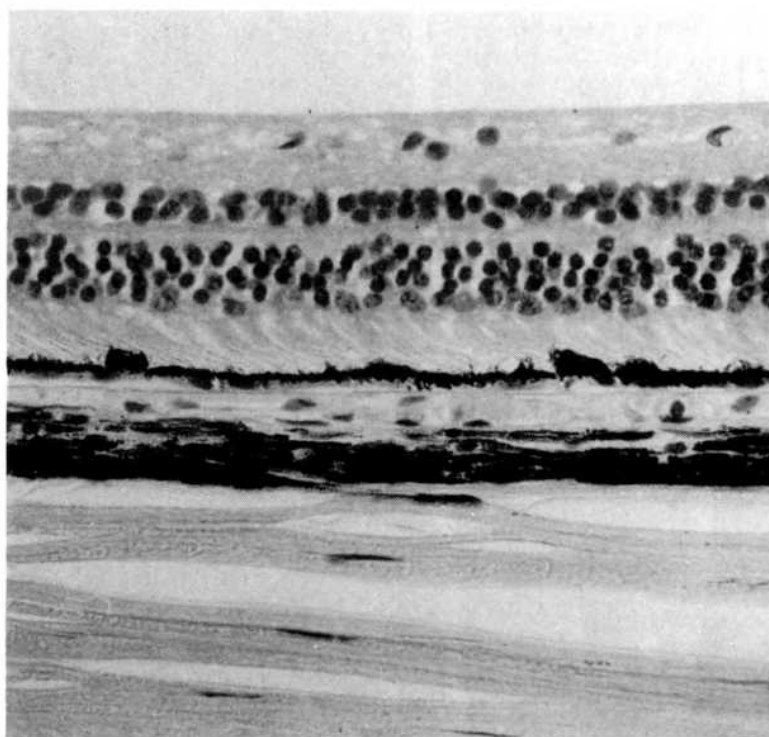




Fig. 4 Degeneration and patchy depigmentation of retinal pigment epithelium (single arrow); the choroid contains many pigmented stromal cells. Pigment-containing cells are also present in the sclera (double arrows). (Perls's stain, $\times 590$).

subnormal. The pattern visual evoked response (VER) showed a reduction in sensitivity, and there was a poor response on the pattern ERG. After the withdrawal of high-dose therapy there was a rapid subjective improvement in vision. Two months later colour vision had returned to normal in each eye. The central scotomas had disappeared and the peripheral field constriction had recovered to within normal limits (Fig. 2). The visual acuity was 6/9 (right) 6/12 (left). The pattern ERG, however, was still subnormal, and there was some loss of scotopic sensitivity.

In August 1983 the patient died of severe congestive cardiac failure. The body was refrigerated and the eye was removed five hours after death. The globe was placed in 3% glutaraldehyde in cacodylate buffer (pH 7.4) after a corneal disc had been trephined out to allow rapid penetration of fixative. Forty-eight hours later small pieces of the retina along with the attached choroid and the sclera were excised from various regions of the globe and post-fixed in 1% isotonic osmium tetroxide. The retina and the choroid were dehydrated in ascending grades of ethanol and finally embedded in araldite. Ultra-

thin sections (50–80 nm) were stained with uranyl acetate and lead citrate, and selected areas were studied with the JEOL-JEM 100C transmission electron microscope. For scanning electron microscopy tissue was dehydrated, critical point dried, sputter coated, and examined in a Hitachi S-520 scanning electron microscope. The remaining portion of the globe was processed for routine paraffin embedding. Sections were stained with haematoxylin and eosin. Perls's stain (Prussian blue reaction) was used to demonstrate deposits of iron in ocular tissues.

Results

Microscopical examination of the whole eye sections (Figs. 3–6) showed deposits of iron in the non-pigmented ciliary epithelium, the ciliary muscle, stromal cells of the choroid, the sclera, and the peripheral retina, which also showed cystoid degeneration. Only occasionally were iron deposits seen in the photoreceptor layer or in the pigment epithelium. The latter showed, however, patchy depigmentation in the equatorial as well as the posterior fundus. In places the retinal pigment epithelium (RPE) cells appeared enlarged and projected into the subretinal space, which sometimes contained detached and rounded up RPE cells containing typical melanin granules. There was no evidence of melanin deposits, however, in the sensory retina around retinal blood vessels.

Scanning electron microscopy (SEM) showed well distributed microvilli on the apical surface of the normal RPE cells. In the equatorial and the posterior regions, where by light microscopy there was evidence of patchy degeneration, with SEM the degenerating pigment epithelial cells showed retraction of villi, or even their total loss, and some of the cells appeared to have large holes (Figs. 7, 8).

Transmission electron microscopy (Figs. 9, 10, 11). The most important changes were observed in the retinal pigment epithelial cells, which showed a variety of structural alterations. Some of the cells had ragged borders, and the basal infolding of plasma membrane had disappeared. The cytoplasm had several alveoli, mitochondria were swollen, and some showed evidence of calcification. The retraction of cytoplasmic extensions produced apparent gaps between cells. Bruch's membrane under the degenerate or depigmented epithelial cells was abnormally thickened and showed the presence of mature elastic tissue, pre-elastic oxytalan fibres, and long-spacing bundles. However, the photoreceptors were normal and did not show any obvious abnormality in either the mitochondria or other organelles.

Fig. 5 The peripheral retina shows cystoid degeneration and contains scattered pigment granules. (Perls's stain, $\times 250$).

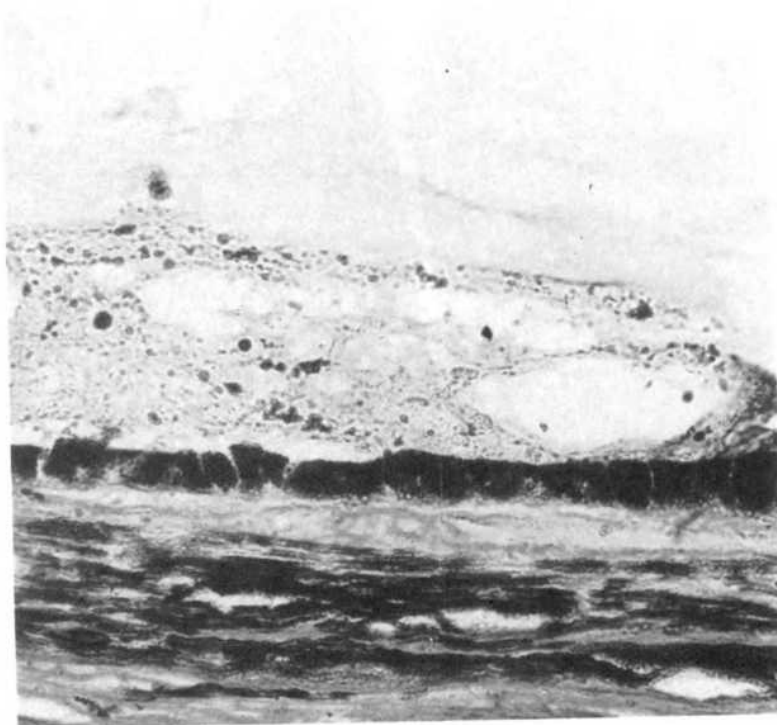


Fig. 6 The non-pigmented epithelium of the ciliary body is filled with iron pigment (double arrows). Similar deposits are also present in the ciliary muscle (arrow). (Perls's stain, $\times 250$).

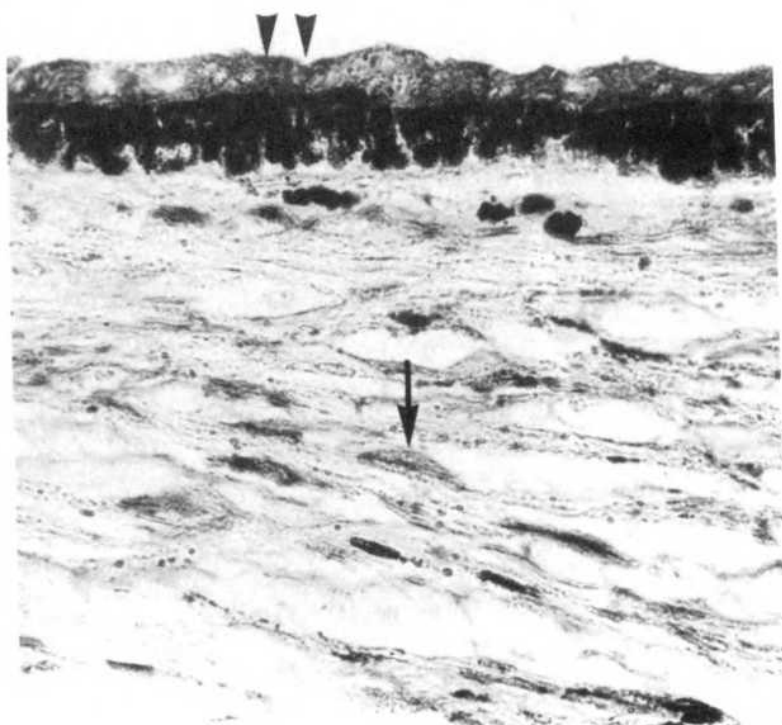




Fig. 7 Scanning electron micrograph of retinal pigment epithelium. (A) Unaffected cells are covered by numerous microvilli. (B) Several enlarged cells (RPE) in the affected equatorial zone of the retina show apparent loss of microvilli. ($\times 6100$).

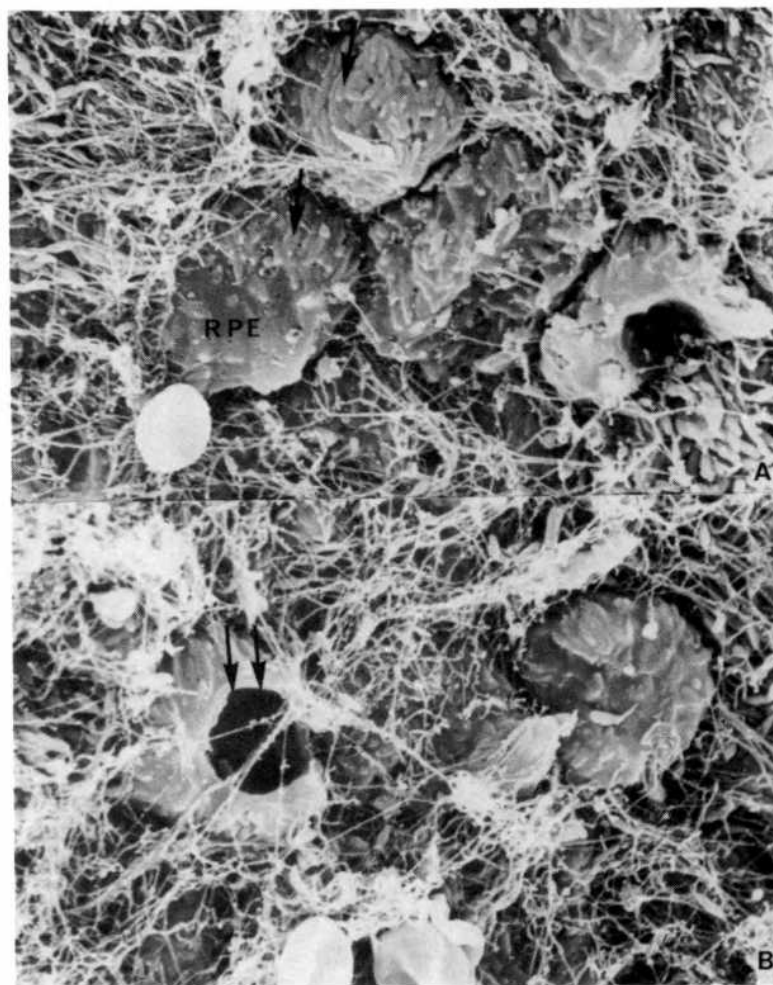
Discussion

A variety of drugs is known to produce retinal toxicity,³ the most important being chloroquine and thioridazine. This is the first time, however, that an eye showing retinotoxicity following administration of a high dose of systemic desferrioxamine has been examined by light and electron microscopy. Clinically detectable lens opacities have been reported before,⁴ but visual failure due to a presumed toxic effect of this drug has only recently been observed.² There are three possible explanations for the changes discovered in the RPE and Bruch's membrane: a simple post-mortem artefact, the effect of ocular siderosis in association with systemic iron overload, or a true toxic effect of the drug desferrioxamine.

We believe that the structural abnormalities were

real rather than post-mortem because the changes in the RPE were patchy, and degenerate cells were always found in the company of apparently normal cells. Furthermore, it has been shown in another scanning electron microscopic study⁵ that eyes processed several hours after death did not show any loss of microvilli on the apical side of the RPE. It could be argued that the artefactual detachment of the retina which occurred during processing may have caused the loss of microvilli seen in the present case. Against this is the observation that similar changes have not been detected in experimental retinal detachment,⁶ although Sakuragawa and Kuwabara have reported⁷ that, if the sensory retina is forcibly pulled out, occasional RPE cells may show total loss of microvilli. Calcification of mitochondria and thickening of Bruch's membrane are definite signs of degeneration and could never be regarded as artefactual. The

Fig. 8. Scanning electron micrograph showing patchy degeneration of retinal pigment epithelium (RPE) as evidenced by retraction of and in some cases apparent loss of surface microvilli in some cells (single arrows). One cell in the lower left corner appears to have burst open (double arrows). ($\times 6100$).



structural changes observed certainly appear more serious than the residual clinical abnormalities, but this is not necessarily contradictory, because lack of correlation between electrophysiological changes and structural alterations in the retina has also been observed in experimental chloroquine toxicity.⁸ It is known that intravitreal injection of desferrioxamine in experimental animals leads to retinal necrosis.⁹ Similarly, animals treated with iodate and iodoacetate show structural changes in the photoreceptors and RPE cells.¹⁰ It is conceded that not all the changes in the RPE may be characteristic of desferrioxamine toxicity, because similar abnormalities in Bruch's membrane have also been seen during the process of aging. The RPE is a highly specialised structure. It has a limited vocabulary with which to express itself in histological and ultrastructural terms, and some at least of the structural alterations

seen in the present case may represent a common endpoint for a variety of pathological processes affecting the RPE.

Whether or not the changes observed in the RPE cells and in Bruch's membrane were in part due to ocular siderosis is difficult to determine, but we believe that their main cause was a toxic effect of the drug desferrioxamine. We take this view firstly because there was clinical recovery of the RPE after treatment with the drug was stopped, whereas withdrawal of desferrioxamine would have been most unlikely to be followed by an improvement had ocular siderosis been the main cause of visual failure. Secondly, systemic iron overload in experimental animals (unpublished observation) fails to produce electrophysiological changes in the retina, suggesting that such overload does not lead to ocular siderosis. Thirdly, in support of the latter observation there was

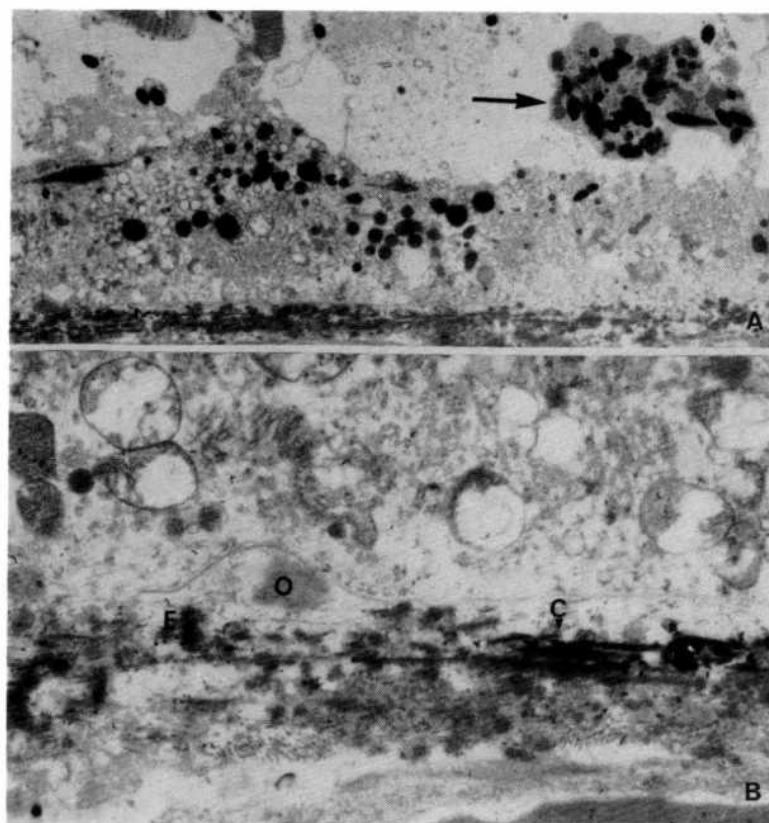


Fig. 9 Transmission electron microscopic appearance of the pigment epithelial cells in the equatorial region of retina. (A) Degenerating RPE; a detached cell (arrow) which contains typical spindle shaped granules is present in the subretinal space. ($\times 2820$). (B) Higher magnification to show swelling of the mitochondria and gross thickening of Bruch's membrane due to accumulation of mature elastic fibres (E); long-standing collagen and pre-elastic oxytalan (O); denatured collagen (C). ($\times 11\,570$).

no evidence of iron deposition in the degenerate RPE cells of the present case. Clinically, therefore, ocular siderosis differs from desferrioxamine toxicity in that, while in the former it is administration of the drug which brings about improvement in vision, in the latter it is its withdrawal.

The mechanism of pigment epithelial damage in this case is not clear. Since desferrioxamine chelates not only iron but also copper, zinc, cobalt, and nickel, it is possible that the visual changes were due to the removal of trace elements from the retina. It is known that urinary excretion of copper and zinc is increased during desferrioxamine infusion. Since copper metabolism appears to be defective in some cases of retinitis pigmentosa,^{11,12} it is possible that the retinal changes in this case were also due to altered levels of copper leading to inadequacy of copper-dependent intracellular oxidative processes.

Low levels of copper in Menkes's disease are associated with an abnormal ERG and VER, defective melanin formation in the RPE, and absence of elastic tissue in Bruch's membrane. Since Bruch's membrane in the present case showed the presence of

both mature elastic tissue and pre-elastic oxytalan fibres, these changes cannot be explained simply on the basis of iatrogenic altered copper metabolism.¹³ Whatever may be the mechanism of retinotoxicity, it would seem that, in patients with iron-overload, prolonged use of desferrioxamine in low doses is without serious ocular consequences.

Possibly the improvement in vision in the present case which followed the withdrawal of high-dose desferrioxamine was associated with limited reversal of the pathological changes. From the clinical and histopathological findings the retinotoxicity produced by a high dose of systemic desferrioxamine would seem to be reversible if diagnosed early. It is therefore important to follow up patients on high-dose therapy ophthalmologically and to detect retinopathy in its earliest stages. The subtle changes may be thought to be unrelated to medication, especially in patients not examined prior to therapy. Although the ERG and EOG are not always abnormal in other forms of retinotoxicity,¹⁴ they may be diagnostic in the toxicity attributable to high-dose intravenous desferrioxamine.

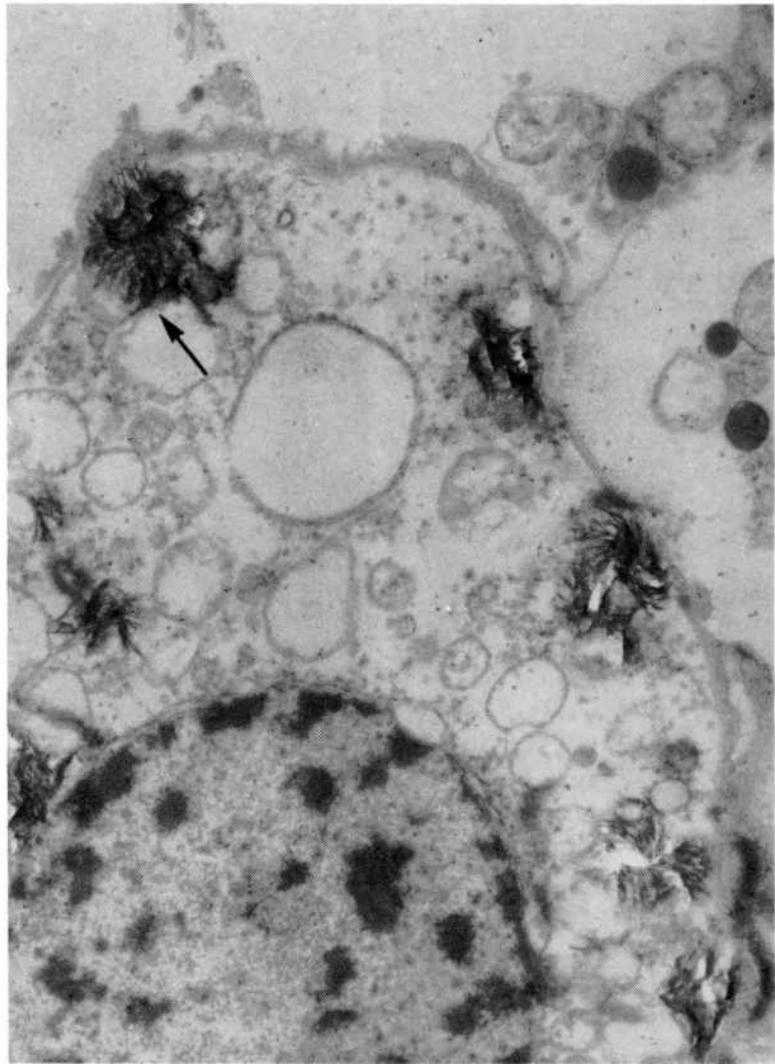


Fig. 10 A retinal pigment epithelium cell in the central retina showing swelling and calcification of mitochondria (arrow). Note that the cell is almost non-pigmented ($\times 14\,400$).

Figs. 1 and 2 are reprinted with kind permission of the Editor of the *Lancet*.

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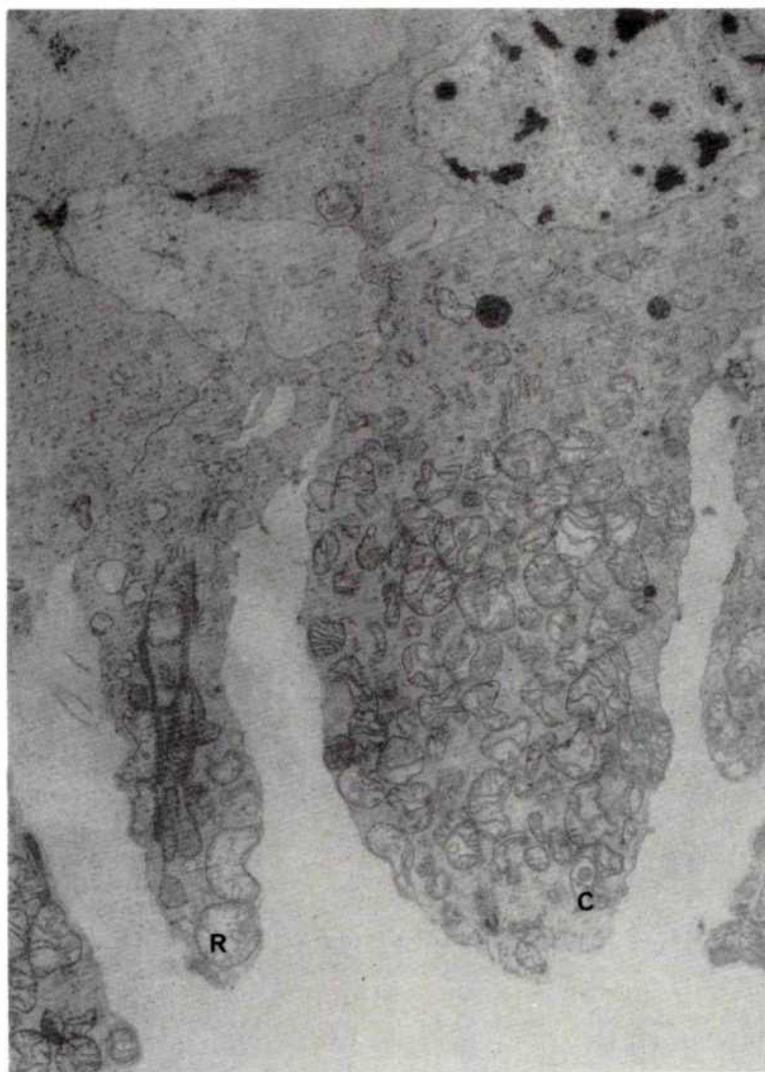


Fig. 11 Transmission electron micrograph showing rod (R) and cone (C) inner segment. Note that mitochondria are well preserved, further supporting the view that changes in the retina were specific, not a post-mortem artefact. The outer segment was artefactually detached during processing. ($\times 5670$).

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One-step extracapsular cataract extraction and silicone oil-injection in the management of proliferative vitreoretinopathy

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SUMMARY A combined technique of extracapsular cataract extraction and silicone oil injection is described. The anterior capsule is preserved to prevent movement of the silicone oil from the vitreous cavity to the anterior chamber. An anterior chamber tap ensures that the vitreous cavity is completely filled with silicone oil, while a peripheral iridectomy prevents postoperative pupillary block glaucoma.

In recent years silicone oil has been used in the treatment of complicated retinal detachments and proliferative vitreoretinopathy.¹⁻⁷ Cataracts are often associated with these conditions.²

The surgical approach for proliferative vitreoretinopathy (PVR) includes a pars plana vitrectomy, membrane peeling, scleral buckling technique, and intravitreal injection of air or gas. If a cataract is present, a pars plana lensectomy may be done at the same time. When intravitreal silicone oil injection is used to tamponade the retina, preservation of the lens capsule is necessary to prevent postoperative anterior segment complications.⁸

We present a one-step procedure for extracapsular cataract extraction and silicone oil injection in the management of cataract and PVR. We believe this is the first report of this combined technique.

Surgical technique

A 4-mm infusion cannula is secured tightly to the sclera entering through the pars plana at the 3 o'clock or 9 o'clock position. A modified Shock phacofragmentor tip is introduced into the lens substance through a second pars plana sclerotomy (Fig. 1A) just posterior to the lens equator. The lens nucleus is fragmented and removed (Fig. 1B). Care is taken to not damage the anterior lens capsule. Removal of the lens cortical material and posterior lens capsule is completed with the Peyman vitrophage (Fig. 1C) by irrigation and aspiration and occasional cutting.

Again extreme caution should be exercised to not damage the anterior lens capsule.

A third pars plana sclerotomy is prepared to introduce the light tube fibreoptic illuminator into the midvitreal. A complete vitrectomy is carried out until all traction has been relieved (Fig. 1D). Any epiretinal membranes present are segmented and removed, if possible. After the vitrophage is removed, the infusion cannula is connected to an air pump system,^{9,10} and a flute needle is introduced through the open sclerotomy to perform a complete air-fluid exchange (Fig. 1E). If any subretinal fluid is present, it can be drained internally at this time. Intraocular pressure is maintained in the 40 to 50 mmHg range to maintain adequate expansion of the globe. The light tube is removed and the sclerotomy is closed securely with appropriate suture material. The flute needle is removed and the sclerotomy is temporarily closed. A scleral buckle is placed to relieve traction and to support the retina.

A wide-bore (16 or 18 gauge) needle connected to a 10 ml syringe containing the silicone oil is introduced through the temporarily closed sclerotomy. An air-silicone oil exchange is performed until a reflux of oil is seen in the infusion cannula (Fig. 1F). The anterior chamber is then tapped with a 30 gauge needle at the limbus, as silicone oil continues to enter the eye¹¹ and to fill the vitreous cavity with the oil (Fig. 1G). The wide-bore needle and the infusion cannula are removed, and the sclerotomies are sutured securely.

A small 2 to 3 mm inferior limbal incision is made with a Zeigler knife. The anterior chamber is then

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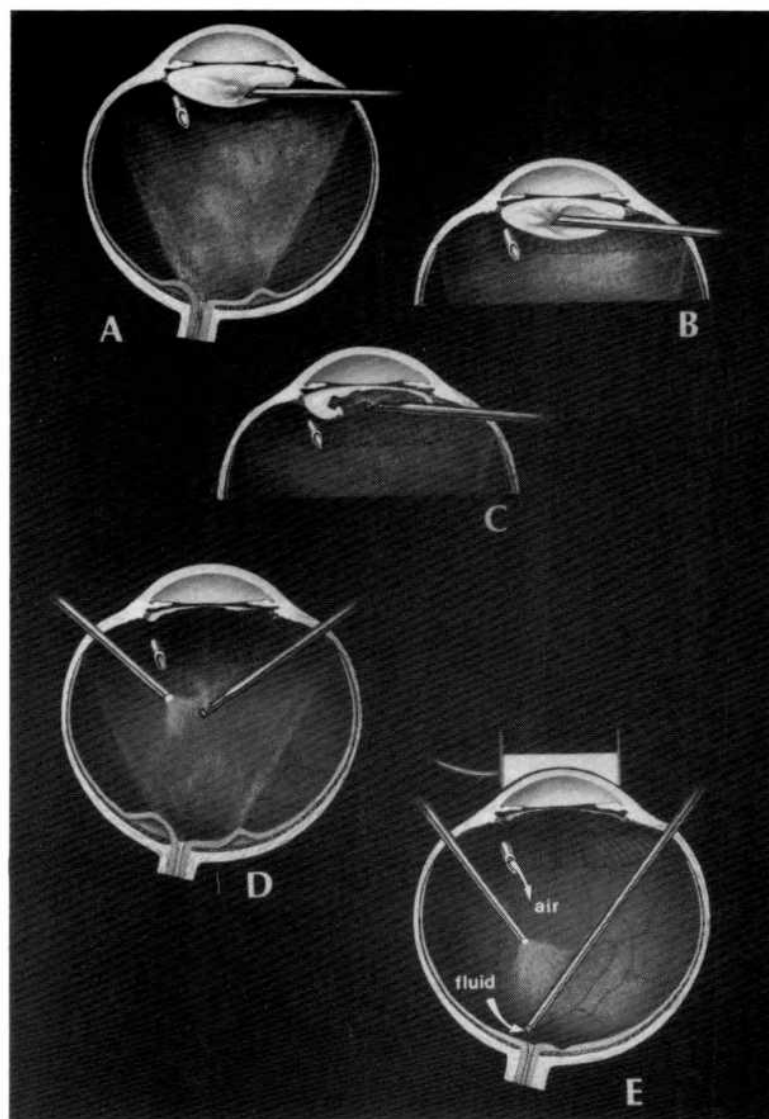


Fig. 1 Artist's rendering of the surgical technique. (A) Introduction of the modified Shock phacofragmentor into the lens substance. (B) Fragmentation of the lens nucleus. (C) Lens cortex and posterior capsule are removed with the Peyman vitrophage. (D) A complete vitrectomy is performed. (E) A complete air-fluid exchange is done with use of a flute needle.

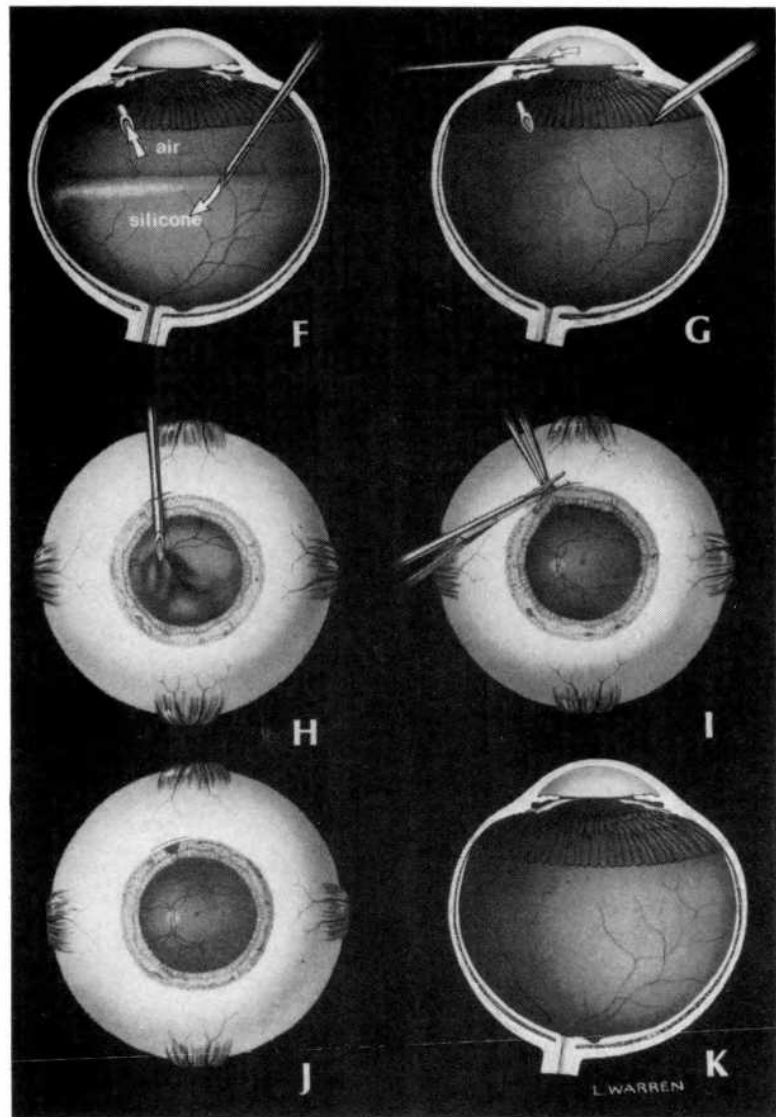
filled with hyaluronic acid (Healon) through a 30 gauge cannula (Fig. 1H). Colibri forceps and Vannas scissors are used to perform a peripheral iridectomy through this incision (Fig. 1I). The iris is then repositioned and the hyaluronic acid is washed out with irrigation solution. The end result is an eye filled with silicone oil; the anterior chamber is protected from the oil by the preservation of the anterior lens capsule (Figs. 1J and K).

Preliminary results

We have performed this combined procedure in

seven patients with good anatomical results (Table 1). The follow-up has ranged between 4 and 8 months. The silicone oil remained confined to the vitreous cavity in all the patients except one. In this patient there was a 3 mm silicone oil bubble in the anterior chamber which had moved through a capsular rent from the vitreous cavity. This occurred on the first postoperative day and had remained stable. The postoperative gonioscopic findings in the patients with increased intraocular pressure are presented (Table 1). The anterior capsule has slightly opacified in two patients. A 1 to 2 mm central neodymium:YAG capsulotomy was performed in

Fig. 1 (cont.) (F) Air-silicone oil exchange is performed with a large-bore needle. (G) Anterior chamber is tapped with a 30 gauge needle to fill the eye completely with silicone oil. (H) Anterior chamber is filled with hyaluronic acid (Healon) (surgeon's view). (I) An inferior peripheral iridectomy is performed (surgeon's view). (J) Surgeon's view. (K) Eye is filled with silicone oil; anterior chamber is free of silicone oil owing to the presence of the anterior lens capsule.



these patients without escape of the silicone from the vitreous cavity into the anterior chamber.

Discussion

We have previously described a technique for removing a cataract in a patient who has silicone oil in the eye (Cohen SB, Peyman GA, de Corral LR, unpublished data). The present technique combines the cataract extraction and the silicone oil injection in one procedure.

The salient feature of this method is the preservation of the anterior lens capsule, which prevents the

displacement of the silicone oil from the vitreous cavity to the anterior chamber. This method decreases the postoperative complications most frequently seen in aphakic patients who have received intravitreal silicone oil, such as glaucoma and keratopathy.^{4,12} Four patients had increased intraocular pressure in the early postoperative period. Only one had silicone oil in the anterior chamber, which moved from the vitreous cavity through a capsular rent. The size of the oil bubble has not increased. In the other three the increased intraocular pressure could be due to peripheral anterior synechiae, inflammation, and hyaluronic acid in the anterior chamber (Table 1).

Table 1 Summary of preliminary results in patients after combined extracapsular surgery and silicone oil injection

Case	Sex	Age	Diagnosis	Preop vision	Preop IOP	Postop vision	Result, anatomical	Postop IOP	Present IOP	Treatment	Postoperative gonioscopic findings
1	M	56	Proliferative diabetic retinopathy; tractional RD OD	OD:CF 1 m	16 mmHg	OD:HM	Retina attached	30 mmHg	18 mmHg	T 0.5%	No oil in AC; Healon in AC
2	M	22	Retinal detachment PVR, giant tear	OD:LP	8 mmHg	OD:LP	Nasal retina elevated; temporal retina attached	9 mmHg	14 mmHg	—	No oil in AC
3	M	34	Car battery explosion trauma OD, RD	OD:LP	7 mmHg	OD:6/50	Retina attached	36 mmHg	6 mmHg	—	Oil in AC through capsular rent; PAS
4	F	21	Proliferative retinopathy secondary to sarcoid; cataract tractional retinal detachment	OD:HM	5 mmHg	OD:HM	Attached nasally, traction over arcades	18 mmHg	8 mmHg	—	No oil in AC
5	M	45	Trauma, macular hole, total RD, PVR; angle recession and scarring 360°	OS:HM	4 mmHg	OS:6/120	Retina attached	37 mmHg	23 mmHg	T 0.5% acetazolamide 250 mg	No oil in AC; 360° angle recession, PAS
6	F	55	Proliferative diabetic retinopathy; retinal detachment	OD:HM	14 mmHg	OD:LP	Retina attached	40 mmHg	6 mmHg	T 0.5%	No oil in AC; inflammation
7	M	74	Proliferative diabetic retinopathy vitreous haemorrhage	OD:HM	17 mmHg	OD: 6/600	Retina attached	15 mmHg	11 mmHg	—	No oil in AC

AC=anterior chamber. PAS=peripheral anterior synechiae. PVR=proliferative vitreoretinopathy. T=timolol. RD=retinal detachment. CF=counting fingers. HM=hand motion. LP=light perception.

The air pump helps to keep the retina attached and the globe expanded so that the silicone oil injection can be accomplished successfully. When the oil injection is combined with the anterior chamber tap, the vitreous cavity can be filled completely with silicone oil. This step is important to prevent an incomplete fill with silicone.

An inferior peripheral iridectomy is done to decrease the possibility of pupillary block glaucoma.¹³ Because silicone oil floats in an aqueous medium, a superior peripheral iridectomy could be blocked by the oil.

Although the mean follow-up time of our patients is short, the preliminary results are encouraging. The cornea has remained clear in all our patients undergoing this procedure. The postoperative rise in intraocular pressure has been managed medically. If any of the preserved anterior capsules become opacified, a small (1 to 2 mm) central capsulotomy with the neodymium:YAG laser may improve the patient's visual acuity. A high viscosity silicone oil (12 500 cSt) does not move readily from the vitreous cavity

through a small capsular opening into the anterior chamber.

Supported in part by core grant 1P3EY01792 from the National Eye Institute, Bethesda, MD.

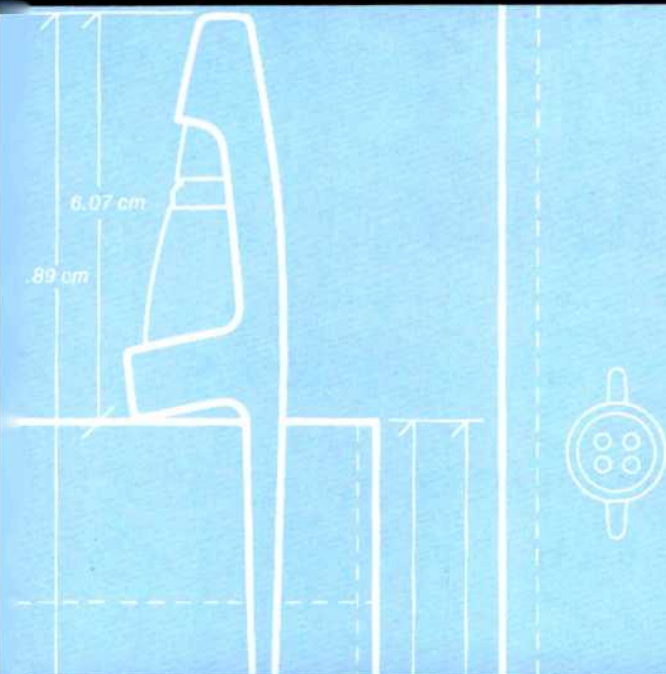
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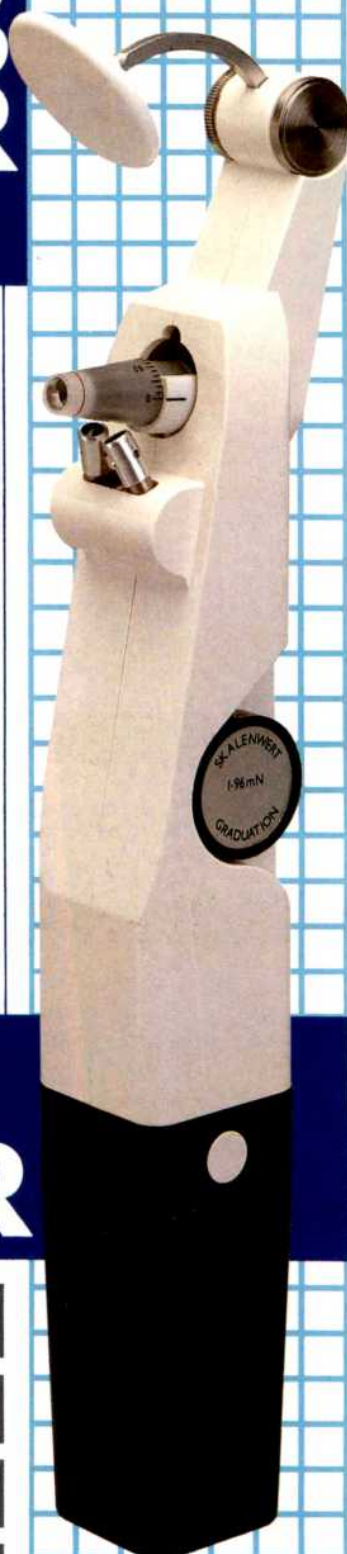
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Respiratory epithelium lined cysts presenting in the orbit without associated mucocele formation

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SUMMARY Three patients presented with orbital cysts lined with upper respiratory tract epithelium. In each case there was no evidence of an associated mucocele. Two patients had a past history of orbital trauma, and the third had had preceding sinus surgery. It is postulated that these cysts were caused by traumatic herniation of nasal sinus epithelium cells into the orbit.

The usual pathological route for upper respiratory tract epithelium to find its way into the orbit is in association with mucocele formation. Mucoceles account for up to 10% of unilateral proptosis.^{1,2} They commonly present in the fourth and fifth decades of life in association with chronic sinus disease, though they may also occur in children with cystic fibrosis.^{3,4}

It is generally accepted that mucoceles form as a result of blockage of the normal drainage pathway of a sinus. Increased pressure, from continuing secretion by the lining of respiratory epithelium, causes sinus expansion and may eventually be associated with osteoclastic resorption of its bony wall. This allows the enlarging respiratory epithelium lined cyst to enter the orbit, with ensuing ocular displacement and proptosis (Fig. 1).

When the diagnosis of mucocele is suspected clinically, radiology is the most useful investigation. The classical signs are well described by Lloyd.⁵ As well as radiological evidence of an increase in size, which may not have been obvious clinically, there may also be opacification of the sinus. The characteristic scalloped margin of the frontal sinus is often lost, and in the ethmoid sinus the typical septate pattern may be eroded. Finally the bony deficit in the sinus wall may become visible.

Successful treatment involves a combined sinus and orbital approach, for it is vital to strip the respiratory epithelium from the wall of the offending sinus and to re-establish a drainage pathway to the nose in order to prevent recurrence.⁶ However, our three patients with orbital respiratory epithelium lined cysts had no evidence of a mucocele or underlying sinus disease at the time of presentation, and no evidence of bony dehiscence or destruction was

found radiologically or at the time of surgery. Effective treatment consisted in excision without recourse to sinus surgery, and there have been no

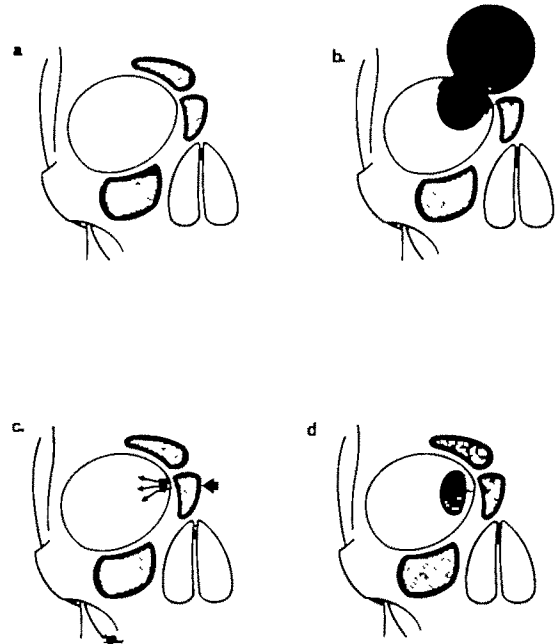


Fig. 1 Proposed pathogenesis of post-traumatic respiratory epithelium lined cysts in the orbit contrasted with orbital mucocele development (a) Normal orbit and nasal sinuses. (b) Frontal sinus mucocele development following blockage of the sinus drainage pathway. (c) Trauma to the sinus region results in the transfer of sinus epithelial cells to the orbit through a small dehiscence/fracture of the orbital wall, (d) with the subsequent development of a respiratory epithelium lined cyst.

Fig. 2 Case 1. Right eye with mass in the superonasal quadrant of the orbit.



recurrences. We consider that another mechanism must be invoked to explain the presence of respiratory epithelium in the orbit.

Case reports

CASE 1

A 26-year-old man presented with a faintly blue cystic mass in the superonasal quadrant of his right orbit. At the age of 12 he had received a blow to his face requiring sutures to a laceration of his right eyebrow. Since then he had noticed a small lump beneath the scar. During the year before he presented the lump had slowly increased in size (Fig. 2). His visual acuity was 6/5. There was no proptosis or ocular displacement. Orbital and sinus x-rays were normal. At surgery a postseptal brown cystic lesion was revealed which leaked oily brown fluid as it was being removed. Posteromedially there was a thin 'tail' from the cyst to the medial wall of the orbit, but no bony defect was seen. Postoperative recovery was uncomplicated.

CASE 2

A 23-year-old man presented with a four-year history of a slowly increasing mass in the superomedial quadrant of his left orbit. Ten years previously he had received a blow to the left brow requiring sutures. The visual acuity was 6/6, and the left eye was displaced inferolaterally but not proptosed. A palpable cystic lesion was present superomedially. Orbital and sinus x-ray views were normal. A CT scan showed an ill defined soft tissue mass in the left orbit (Fig. 3).

At surgery a subperiosteal cystic lesion was revealed overlying the ethmoid sinus. It was dissected free and found to contain brown oily fluid. There was

no obvious bony defect. The patient made an uncomplicated recovery.

CASE 3

A 20-year-old man presented with a 10-month history of a slowly increasing mass in the inferomedial quadrant of his right orbit. Eighteen months previously he had had a right sided maxillary sinus washout procedure. There had been several episodes of painful increase in size of the mass over the 10 months before presentation. The visual acuity was 6/6 and the right eye was displaced superolaterally and proptosed 2 mm. A faintly blue cystic lesion was present inferomedially (Fig. 4).

Orbital and sinus x-rays were normal; in particular



Fig. 3 Case 2. Axial CT scan with ill-defined soft tissue mass medial to the left eye (arrowed).



Fig. 4 Case 3. Right eye with mass in the lower inner quadrant of the orbit.

there was no sinus clouding. CT scans revealed a soft tissue mass in the right orbit. At surgery a postseptal brown cystic lesion was revealed. It contained brown oily fluid and there was a thin 'tail' from the cyst to the medial wall, but no bony defect was seen. Post-operative recovery was uncomplicated.

PATHOLOGY

The histopathological examination of the three orbital lesions showed each to be a thin walled cyst lined by a pseudostratified columnar epithelium containing scattered mucin-producing cells (Fig. 5).

There was evidence of focal epithelial atrophy, possibly due to pressure effects. In case 2 there were subepithelial foci of active chronic inflammation, with many macrophages containing lipid material, indicating a response to leaked cyst contents (Fig. 6). In areas of the epithelium associated with a heavy chronic inflammatory response there was metaplasia

of the pseudostratified columnar epithelium to squamous epithelium. No epidermis or dermal appendages were present within the wall of any of these cysts, ruling out a diagnosis of dermal inclusion cyst or dermoid.

Discussion

The preoperative differential diagnosis in our first two cases included orbital varices or an implantation cyst, and we were surprised to find cysts lined by upper respiratory tract epithelium in the absence of an underlying mucocele. However, the characteristic clinical picture of a young man presenting with a post-traumatic, faintly blue cystic lesion lying in the medial orbit, with normal orbital x-rays, enabled us provisionally to diagnose our third case pre-operatively. In the two cases preceded by trauma to the region our hypothesis is that a tiny fracture or dehiscence allowed herniation of nasal sinus epi-

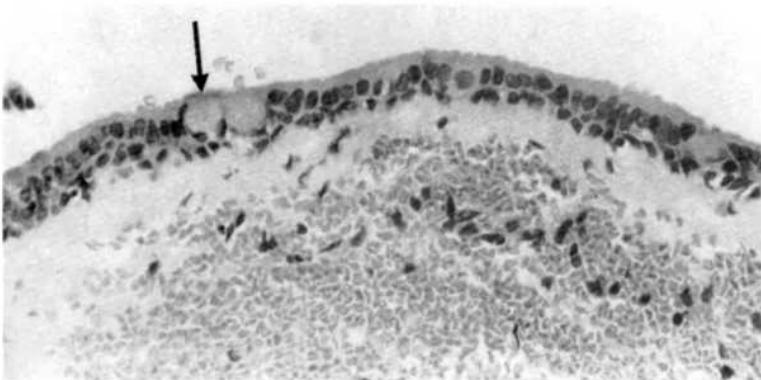


Fig. 5 Microscopic appearance of the cyst lining (case 3), comprising pseudostratified columnar epithelium with an occasional mucin-secreting goblet cell (arrow) (H and E, $\times 122$).

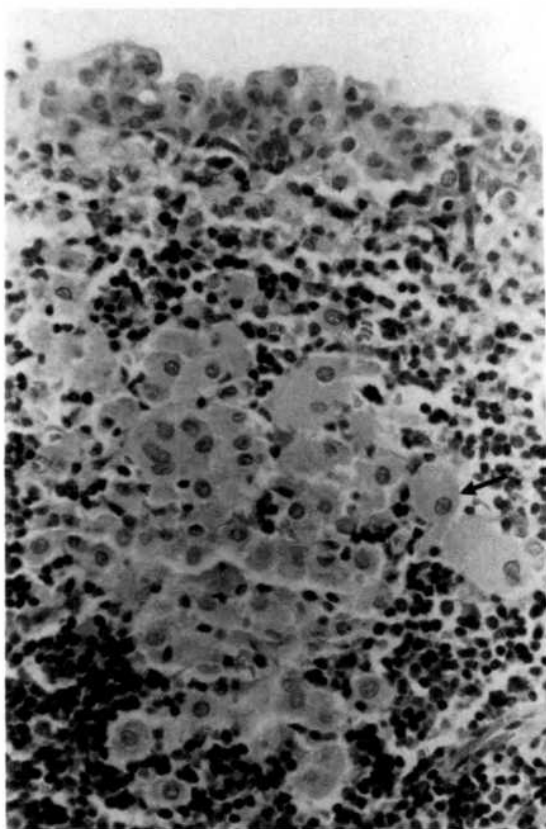


Fig. 6 Cyst lining (case 2) showing squamous metaplasia, and dysplasia of the epithelium, with underlying chronic inflammation which includes many macrophages (arrowed). (H and E, $\times 128$).

thelial cells into the orbit, with the subsequent development of a slowly growing cyst (Fig. 1). The third case could be related to underlying sinus disease which had subsequently resolved by the time of ophthalmic presentation. However, we feel the trauma of the maxillary antral washout may have had the same herniating effect as we have proposed for accidental trauma.

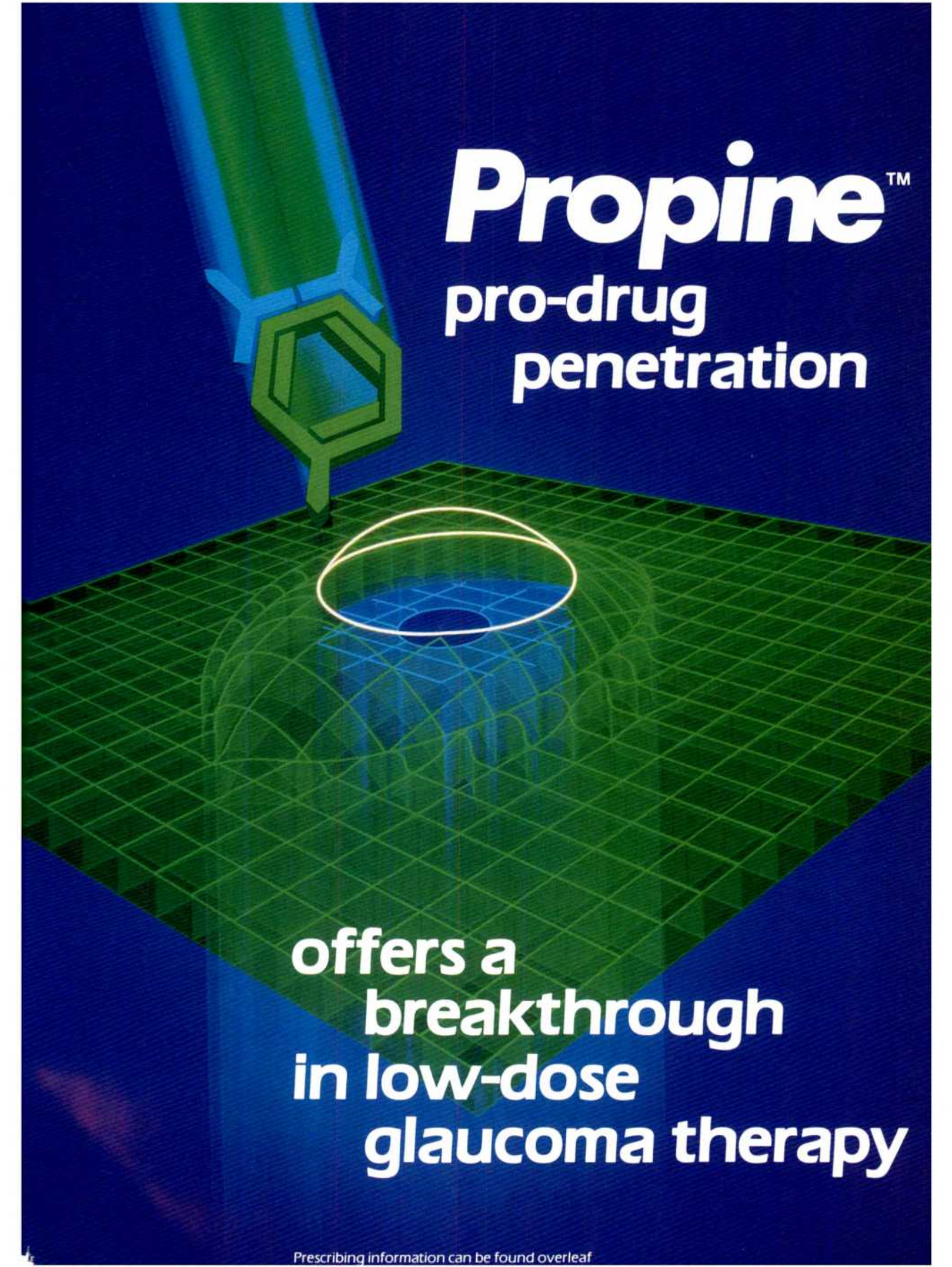
In summary, while cysts lined with upper respiratory tract epithelium classically occur in the orbit as a result of mucocoele development, we have described three young men with orbital cysts lined with upper respiratory tract epithelium following trauma in whom no evidence of mucocoele was found. Straight-forward excision resulted in a good prognosis, and there have been no recurrences.

Our thanks are due to Mrs Sarah Cole for typing the manuscript, to Mr A R Elkington for referring case 2, and to Dr E H Burrows for providing copies of the CT scan (Fig. 3).

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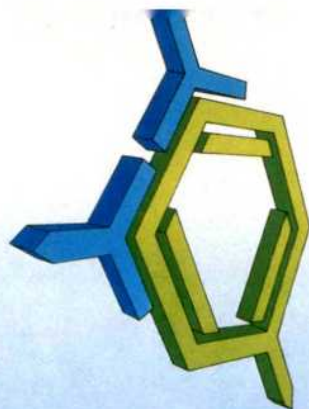


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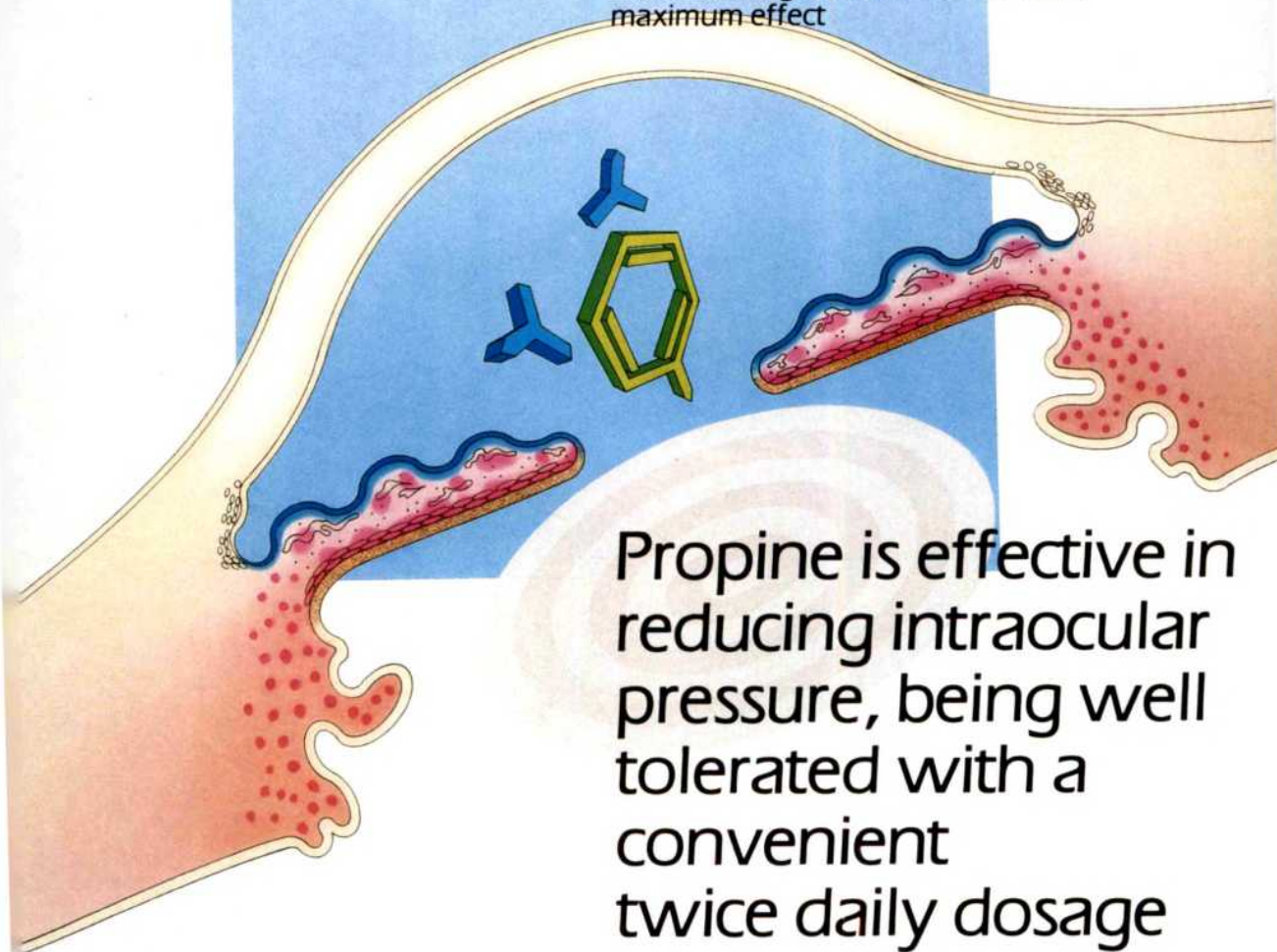
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Cryptophthalmos: surgical treatment of the congenital symblepharon variant

D J BRAZIER, S J HARDMAN-LEA, AND J R O COLLIN

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SUMMARY A case of the congenital symblepharon variant of cryptophthalmos is reported. Surgical treatment is described. The ophthalmic features of cryptophthalmos and its systemic associations are reviewed.

The term cryptophthalmos was introduced by Zehender¹ and Manz² in 1872 when they described a child whose eyes were covered by continuous sheets of skin extending from forehead to cheeks. Emburger *et al.*³ attributed the earliest description to Saint-Hilaire in 1832. This paper reports the clinical features and early surgical management of the variant of cryptophthalmos to which François⁴ gave the name 'congenital symblepharon.'

Case history

A female child was born by spontaneous vaginal delivery at 40 weeks gestation to non-consanguineous parents. She was the first child of both parents. The baby was immediately noted to have a marked abnormality of the left upper eyelid involving absence of the lid margin and lashes, with adherence of the lid skin to the upper one-third of the cornea (Fig. 1 and 2). The upper lacrimal punctum was absent. The lower lid and fornix were normal and the punctum present. The lower two-thirds of the cornea and the remainder of the anterior segment appeared normal. The right eye and lids showed no abnormality.

Other abnormalities were also present. The left temporal region appeared depressed, and the left eyebrow was replaced by a downward sweep of the frontal hairline (Fig. 1). The ears were of a simple pattern, low-set, and had narrow external meati. The nose was dimpled at the tip and the left nostril notched. The frenulum of the tongue was short and respiration noisy owing to variable laryngeal stridor. There was syndactyly in both hands (Fig. 3), but in other respects the limbs appeared normal. No other

abnormalities were detected on examination of chest, abdomen, and external genitalia. Skull and chest radiographs were considered to be within normal limits.

The adhesion of the upper lid to the cornea was responsible for extensive corneal exposure, which



Fig. 1 Age 5 days. The left upper lid has no lashes or defined margin and is adherent to the underlying globe. The left eyebrow is replaced by a downward extension of the frontal hairline.

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Fig. 2 Age 5 days. The central corneal infiltrate and overlying epithelial defect are visible. The left nostril is notched.



was initially treated conservatively by the hourly application of chloramphenicol eye ointment. During the following days, while a more detailed paediatric assessment was made, a corneal epithelial defect with increasing stromal infiltrate appeared in clear cornea adjacent to the margin of the upper lid skin. Surgical intervention was thought to be required to ensure corneal protection, and the child underwent a procedure involving a lid rotation flap, as described by Mustardé,⁶ when six days old.

Examination under anaesthesia confirmed the pre-operative findings on the left and that the right eye,

including the fundus, was normal. A skin incision was made adjacent to the skin edge where the left upper lid met cornea and conjunctiva (Fig. 4a). The skin was freed from grey upper cornea and adjacent sclera. A rudimentary levator palpebrae superioris muscle and normal superior rectus muscle were identified. A full thickness incision was made in the lower lid starting lateral to the punctum, sweeping down in an arc to the inferior extremity of the lower fornix and back up almost to the lid margin at its midpoint (Fig. 4a). Care was taken to preserve the marginal artery of the lid. The medial end of the lower lid was then rotated through 180° round the hinge, consisting of full thickness tarsus and the marginal vessels, to produce a small laterally placed palpebral aperture (Fig. 4b). The conjunctiva of the new upper lid was attached to the superior rectus insertion and the levator aponeurosis sutured to the tarsus of the rotated lid segment to provide some mobility. Residual edges of conjunctiva and skin were closed with collagen sutures (Fig. 4c). Post-operative recovery was uncomplicated, and the wounds healed satisfactorily (Fig. 5).

Three weeks later the bridge of tarsus linking upper and lower lids was divided and the lid margins resutured. The corneal epithelium had healed, but the central and superior stromal opacity persisted. There was some movement of the reconstructed upper lid, and, although the lids remained slightly open during sleep, corneal protection was much improved. No further corneal ulceration developed with a regimen of chloramphenicol eye ointment six hourly.

During this period the child had been fully assessed. Chromosome studies were normal. Micro-



Fig. 3 Syndactyly, right hand. The left hand was similar.

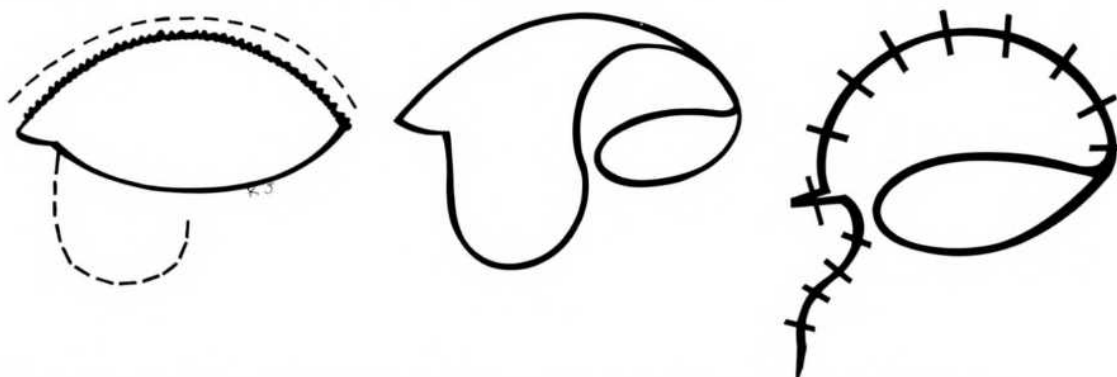


Fig. 4 Lid rotation flap. (a) Rotation incisions. (b) Rotation of medial end of lower lid. (c) Skin edges sutured.

laryngoscopy revealed that the arytenoids were fixed together in the midline posteriorly, giving rise to a narrow glottic slit. No subglottic stenosis of the trachea was identified. Renal ultrasound showed the kidneys to be present but small (right 3.4 cm, left 3.5 cm, expected size 4.0 cm). Corticomedullary distinction was normal, and no cysts were present. Blood urea and creatinine levels were normal. A micturating cystourethrogram showed no abnormality of ureters, bladder, or urethra. Tight anal stenosis required dilatation under general anaesthesia.

When the baby was examined at the age of 4 months the left lids were soundly healed (Fig. 6). Some upper lid symblepharon persisted, but the cornea was stable and ocular lubricants were not required. Visual attention with the right eye was normal, and closure of the left eye was observed when this eye alone was exposed to bright light. A

haemangioma of the upper lip had developed and was causing minor feeding problems (Fig. 7).

Flash visually evoked responses and an electroretinogram, without sedation or anaesthesia, showed cortical responses of normal amplitude and latency and a well defined retinal response from both eyes.

The child remains under regular review and will almost certainly require further division of upper lid symblepharon with mucous membrane grafting when older.

Discussion

Since its description by Zehender and Manz most information regarding cryptophthalmos has been recorded in the form of case reports. The most comprehensive review of the ocular condition and its recognised systemic associations is that published



Fig. 5 Age 1 month (27 days after rotation flap).

Fig. 6 Age 4 months, three months after division of tarsal bridge between left lids. Inferior cornea healed.



by François.⁴ Cryptophthalmos in association with these specific systemic features is called, by various authors, cryptophthalmos syndrome, François syndrome, or Fraser syndrome.^{6,7} François reviewed 41 cases from the literature and added two new ones. He divided the ophthalmic signs into three groups:

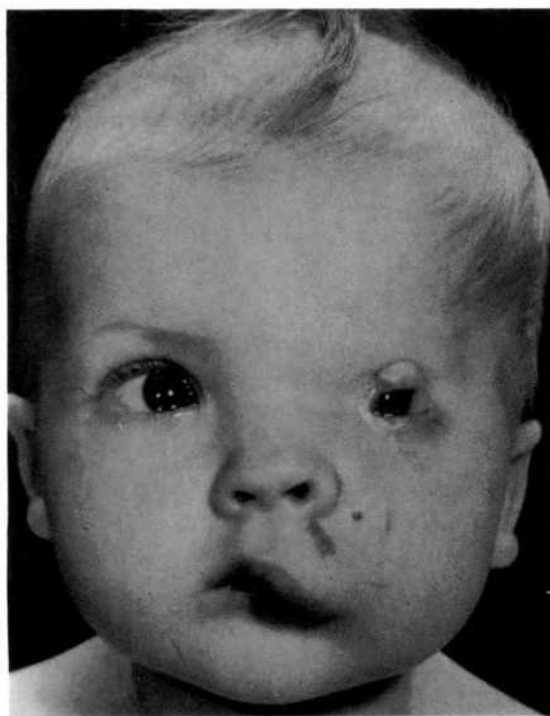


Fig. 7 Age 4 months. Haemangioma of upper lip present.

1. *Complete (typical) cryptophthalmos.* The lids are replaced by a sheet of skin running from forehead to cheek with absence or poor development of the eyebrow. No lashes or gland structures can be identified. The covered globe gives rise to an elevation in the overlying skin which moves when eye movements occur. The skin is adherent to the underlying cornea and there is no conjunctival sac. Microphthalmos is usual.

2. *Incomplete (atypical) cryptophthalmos.* Rudimentary lids are present, with a small conjunctival sac placed laterally. The palpebral aperture is about one-third of normal length. The globe is usually small and almost completely covered by skin.

3. *Abortive form or congenital symblepharon.* The upper lid, without a defined margin, covers and adheres to up to 75% of the upper cornea. The lid has no punctum and there is no upper conjunctival fornix. The free part of the cornea may be keratinised and opaque. The globe is usually of normal size but may be small.

The ophthalmic features of the reported case therefore appear to be typical of the congenital symblepharon variant of cryptophthalmos and in almost all respects identical to those of cases published by François (observation II),⁴ Key,⁸ and Sugar.⁹ These three patients were considerably older when reported, being 3, 12, and 35 years respectively. While the uncovered portion of the cornea in our case was clear at birth, it appears that keratinisation and opacity of the cornea may occur before birth. Emburger *et al.*³ reported a post-mortem study of a stillborn infant of 7 months gestation with multiple malformations including left congenital symblepharon. Microscopically this cornea proved to be

vascularised and covered with partially keratinised stratified squamous epithelium. In the cases of François, Key and Sugar the inferior extremity of the cornea appears to be relatively clear. This may be explained by maintenance of the tear film and protection by the lower lid.

Previous detailed reports of congenital symblepharon^{4,12} do not include accounts of lid surgery designed to protect the exposed cornea. An account of surgical exploration in complete cryptophthalmos is provided by Gupta and Saxena,¹¹ and surgical treatment of incomplete cryptophthalmos is described by Waring and Shields.¹² The latter authors extended the small palpebral aperture medially by incision and dissection of the skin from the underlying globe. A conformer was placed to maintain the fornices. No details of follow-up were given.

The systemic associations of cryptophthalmos have been reviewed by various authors including François⁴ and Ide and Wollschlaeger.¹³ These associated anomalies are known to include abnormalities of head shape, nose and ears, meningoencephalocele, hare lip and cleft palate, syndactyly, genital anomalies, and a miscellaneous group of defects including atresia of larynx, kidneys, bladder and anus, and umbilical hernia.

It seems likely that complete cryptophthalmos arises in the embryo because of total failure of lid fold development.^{1,2,14} The ectoderm overlying the cornea is converted into skin and no conjunctival sac formed. The congenital symblepharon variant may result from failure of the portion of lid fold derived from the frontonasal process while the portion derived from the maxillary process develops normally. This would explain the abnormal upper lid and normal lower lid. Perhaps subnormal development of the whole lid fold gives rise to the incomplete form of cryptophthalmos.

There is considerable evidence to suggest an autosomal recessive mode of inheritance for cryptophthalmos syndrome, and there are a number of reports of multiple cases occurring in some fami-

lies.^{4,15} Genetic counselling of couples with affected children seems advisable.

We thank Mr R Butler for referring the patients and our many colleagues at Great Ormond Street who helped with her management, particularly Dr J Burn of the Department of Medical Genetics. We also thank Karen Johnstone for drawing the diagrams and all the members of the departments of medical illustration at Great Ormond Street and Moorfields who took and prepared the photographs. We are grateful to Mr T J Pfyfche for his help with translation of the German papers.

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Chronic lymphangiectasis in Turner's syndrome

HENRY D PERRY AND ALFRED J COSSARI

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SUMMARY A 3½-year-old female presented with Turner's syndrome and Nonne-Milroy-Meige disease. Ocular findings included strabismus and bilateral chemosis which was unchanging and persisted throughout the four years the patient was followed up. Histopathological findings included diffuse lymphangiectasia and dense connective tissue surrounding the dilated lymph channels. Although the association between congenital lymphoedema and Turner's syndrome is common, the lymphoedema usually disappears by the first year of life. The persistence of the lymphoedema beyond this age is rare, as is the presence of the persistent chemosis. This report represents the first histopathological documentation of congenital lymphangiectasis in association with Turner's syndrome.

In 1938 Turner described a chromosomal anomaly in which there are 45 chromosomes due to the absence of the second sex chromosome.¹ Females with Turner's syndrome have numerous features such as short stature, webbed neck, shield shaped chest, cubitus valgus, amenorrhoea, and infantile sexual development. Recently we have encountered a patient with Turner's syndrome and Nonne-Milroy-Meige disease. This is the first time the association between Turner's syndrome and congenital lymphoedema has been reported with ocular findings and histopathological confirmation.^{2,3}

Case report

A 3½-year-old white female with Turner's syndrome (karyotype XO) was referred for ophthalmic examination. She was referred because of a vision defect, and the family pediatrician noted that she was holding things very close. According to her history the patient did not open her eyes until 7 weeks of age owing to swelling and ophthalmia neonatorum. She had developmental delay and was attending a special school for handicapped children. Anomalies included bilateral inguina hernias, bladder hypotony, congenital hip dysplasia, and congenital lymphoedema.

Ocular examination in May 1980 showed the vision to be 20/200 OD and 20/200+1 OS. External exam-

ination showed a very apprehensive, short 3½-year-old white female with a prominent webbed neck. (Fig. 1). Cycloplegic refraction OD +3.50–5.50 axis 90°, OS +2.25–5.50 axis 90° improved the vision to



Fig. 1 Full face external photograph showing nasal conjunctival cysts, oedema of the right eye, and prominent webbed neck.

Correspondence to Henry D Perry, MD, 2000 North Village Avenue, Rockville Centre, NY 11570, USA.

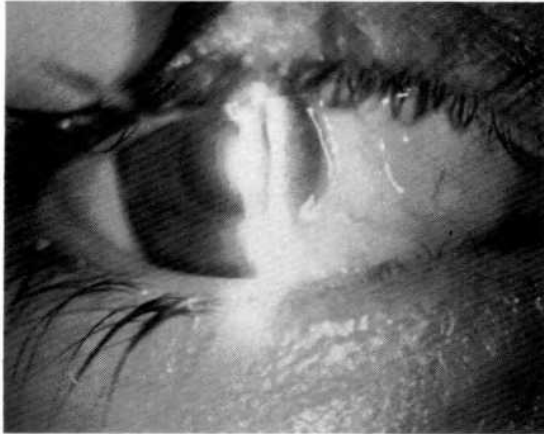


Fig. 2 Slit-lamp photograph of the right eye showing diffuse conjunctival oedema of the nasal conjunctiva.

20/60 OU. There was a constant A pattern exotropia of 35 prism dioptres and a bilateral ptosis, OS greater than OD. Slit-lamp examination of the anterior segments revealed diffuse conjunctival oedema with bullae present nasally OD and temporally OS (Fig. 2). The rest of the ocular examination, including examination of the fundus under dilatation, was unremarkable. Further external examination revealed left hand and right pedal lymphoedema (Fig. 3 and 4).

A diagnosis of Nonne-Milroy-Meige disease was made from the association between the conjunctival

chemosis and lymphoedema in the left hand and right foot. In August 1980 the patient underwent a bilateral 7 mm recession of the lateral rectus muscles with half tendon infrapacements. A conjunctival biopsy was taken at the time of surgery from the right eye and fixed in 10% buffered formalin. The patient did well postoperatively except for a small dellen located temporally on the left cornea, which cleared up by the second postoperative week. After four years of follow-up the patient has a monofixational microexotropia with best corrected visual acuities of 20/30— in each eye.

The conjunctival specimen measured 1×3 mm and was pale white. The specimen was embedded in paraffin and sections were stained in Haematoxylin and eosin, periodic acid Schiff, Masson trichrome, Verhoeff-van-Gieson, and von Kossa stains. Haematoxylin and eosin showed the conjunctival epithelium to be unremarkable. Pertinent findings were limited to the substantia propria, where there were multifocal areas of dilated vascular channels with delicate septa lined on both sides by non-contiguous, flattened endothelial cells. Most of the spaces contained acellular fibrinous debris with only occasional red blood cells noted. The surrounding stromal collagen fibres were thickened and proved to be the most striking differentiating feature from normal conjunctiva. This thickened stroma resembled that seen in conjunctival dermoids, (Fig. 5 and 6). The supplementary stains added nothing.

Discussion

The ophthalmic disorders in Turner's syndrome include hyperopia, myopia, ptosis, cataracts, strabismus epicanthus, hypertelorism, blue sclera,

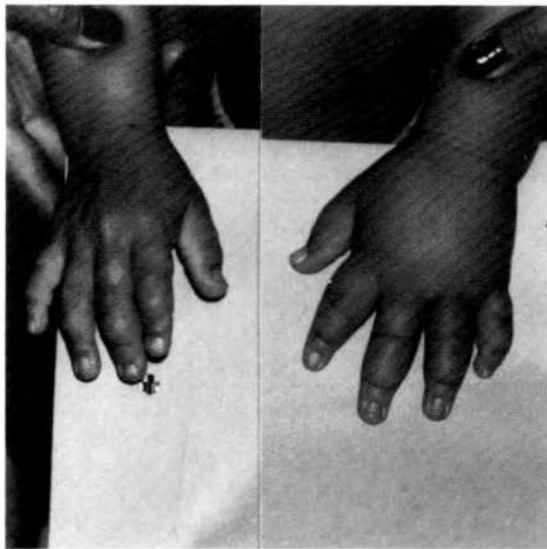


Fig. 3 External photograph of both hands showing marked oedema of the right 2, 3, 4 fingers and of the entire left hand and wrist.



Fig. 4 External photograph of lower extremities showing severe oedema of both feet and ankles.

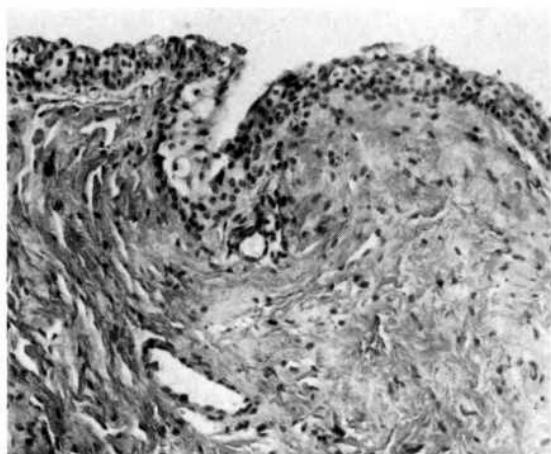


Fig. 5 Relatively normal bulbar conjunctiva lying over a thickened substantia propria with a prominence of dense connective tissue. (Haematoxylin and eosin, $\times 30$).

anti-Mongolian slant, red-green colour blindness, exophthalmos, choroidal coloboma, persistent pupillary membrane, microcornea, microphthalmos, nystagmus, absence of the caruncle, diminished



Fig. 6 Several dilated lymph channels are noted in the dense connective tissue of the conjunctiva. (Haematoxylin and eosin, $\times 37$).

retinal pigmentation, lid haemangioma, abducens palsy, retinitis pigmentosa, hypoplasia of the lacrimal gland, oval cornea, and Duane's syndrome.¹ Here we report the occurrence of chemosis and an ophthalmic finding not previously recorded. The chemosis was chronic and unchanging in amount and degree in the four years the patient was followed up.

The association between Turner's syndrome and congenital lymphoedema is not uncommon. Hereditary lymphoedema with an onset at or near birth has been termed Milroy's disease, while that of later onset is referred to as Meige's disease.⁵ In Izakovic's study of 26 children with congenital lymphoedema 18 out of 22 girls had the 45 X karyotype.⁶ Henriksen reported two cases of Turner's syndrome associated with congenital lymphoedema in newborn babies.⁷ In their study of lymph vessel defects in patients with ovarian dysgenesis Vittay and co-workers⁸ mention the occurrence of the lymphatic defects in patients with Turner's syndrome. They argue that the defects are no more common in Turner's syndrome than in other cases of ovarian dysgenesis. The persistence of lymphoedema beyond the first year of life is unusual according to Gordon *et al.*⁹ The occurrence of conjunctival lymphoedema is rare, as is the occurrence at a young age.¹⁰ Klein and Doret reported a case of congenital lymphoedema with the development of chemosis at age 50.¹¹ Tabbara and Baghdassarian reported on a 7-year-old girl with congenital lymphoedema of the conjunctiva and of the extremities.² This girl also had moderate amblyopia of the right eye and esotropia. However, they described the patient as otherwise normal. A requested biopsy was refused by the patient's family. Our patient thus presented an unusual opportunity to evaluate the conjunctival changes of Nonne-Milroy-Meige disease in association with Turner's syndrome. The occurrence of lymphoedema at a young age should suggest Turner's syndrome.^{3,12}

Histopathologically our findings of dilated lymph channels with thin endothelium lined walls is similar to previous reports of Milroy's disease in the lower extremities. In addition these reports also stressed prominent fibrosis, which in our case appeared very much like the thickened collagen fibres characteristic of a conjunctival dermoid. Over all, the histopathological features were distinctive, and the presence of the thickened collagen fibres allowed the condition to be differentiated from a lymphangioma.

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Correspondence

Extracapsular lens extraction

SIR, We congratulate Jeffrey L. Jay on his paper¹ and would like to confirm his findings from our own experience. We have on record 13 cases of this triple procedure by Dr Arthur SM Lim with a similar follow-up (2–34 months, average 17 months). Our procedure is similar to Mr Jay's, differing only in the positioning of the corneoscleral incision (centred on 12 o'clock in our case) and the choice of intraocular lens—Sinskey style—positioned within the capsular bag. In answer to his question regarding flexible loops, we do not find that the absence of "rigid legs acting as radial struts" leads to shallowing of the anterior chamber.

We agree that it is indeed possible to offer patients the benefit of combining intraocular lens implantation with glaucoma surgery in selected cases.

PATRICIA HART

Eye Clinic,
National University Hospital,
Singapore

Reference

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Book reviews

The Fundus Periphery. Report of the French Society of Ophthalmology. By P. BEC, M. RAVAUULT, J.-L. ARNE AND C. TREPSAT. Pp. 431. No price given. Masson: Paris. 1985.

The periphery of the ocular fundus is an area of great clinical importance and great anatomical complexity. It has been the subject of many authoritative but contradictory reports, and it is presumably for this reason that the French Ophthalmological Society asked for a scholarly report to review our present knowledge.

The annual reports of the French Ophthalmological Society have a splendid tradition, and this book lives up to their reputation. It is a product of two centres, Toulouse and Lyons, and is written by a number of authors from those centres with scholarship, industry, and modesty. The fact that Dr Blodi has undertaken the formidable task of translating this work is a compliment to their efforts.

The book consists of two parts—the periphery of the normal ocular fundus, and the pathology of the peripheral ocular fundus, the first 100 pages being devoted to the normal fundus. In the pathological section the longest and most important chapter relates to degenerative lesions, but, rightly or wrongly, chapters devoted to inflammation, vascular anomalies, tumours, etc. are also included. Al-

though in the French edition all the colour pictures were put at the back of the book for reasons of economy, it is a pity this decision was not reversed in the English edition. Overall, however, the book succeeds in clarifying a confused subject and is an excellent source of references. It could usefully be read by everyone who has pretensions to treating the peripheral fundus either therapeutically or prophylactically.

R. K. BLACH

Notes

Implant lens congress

The Fifth Congress of the European Intraocular Implant-lens Council will take place in Jerusalem, Israel, on 13 to 18 September 1987. Further information from: Secretariat, PO Box 50006, 61500 Tel Aviv, Israel.

Study grants

Glaucoma Group Travel Fellowship. Sponsored by Merck Sharp and Dohme, this will assist a visit to a hospital or research centre during the academic year starting 1 October 1986. The award will be equivalent to £1500. The purpose of the award is to enable the successful applicant to gain experience and knowledge in pursuit of a specific project related to glaucoma.

Glaucoma Group Research Grant. Sponsored by International Glaucoma Association, this will be available for a clinically orientated research project related to glaucoma for 1986. The award will be equivalent to £2500. It may be used towards salary or project expenses or for buying equipment.

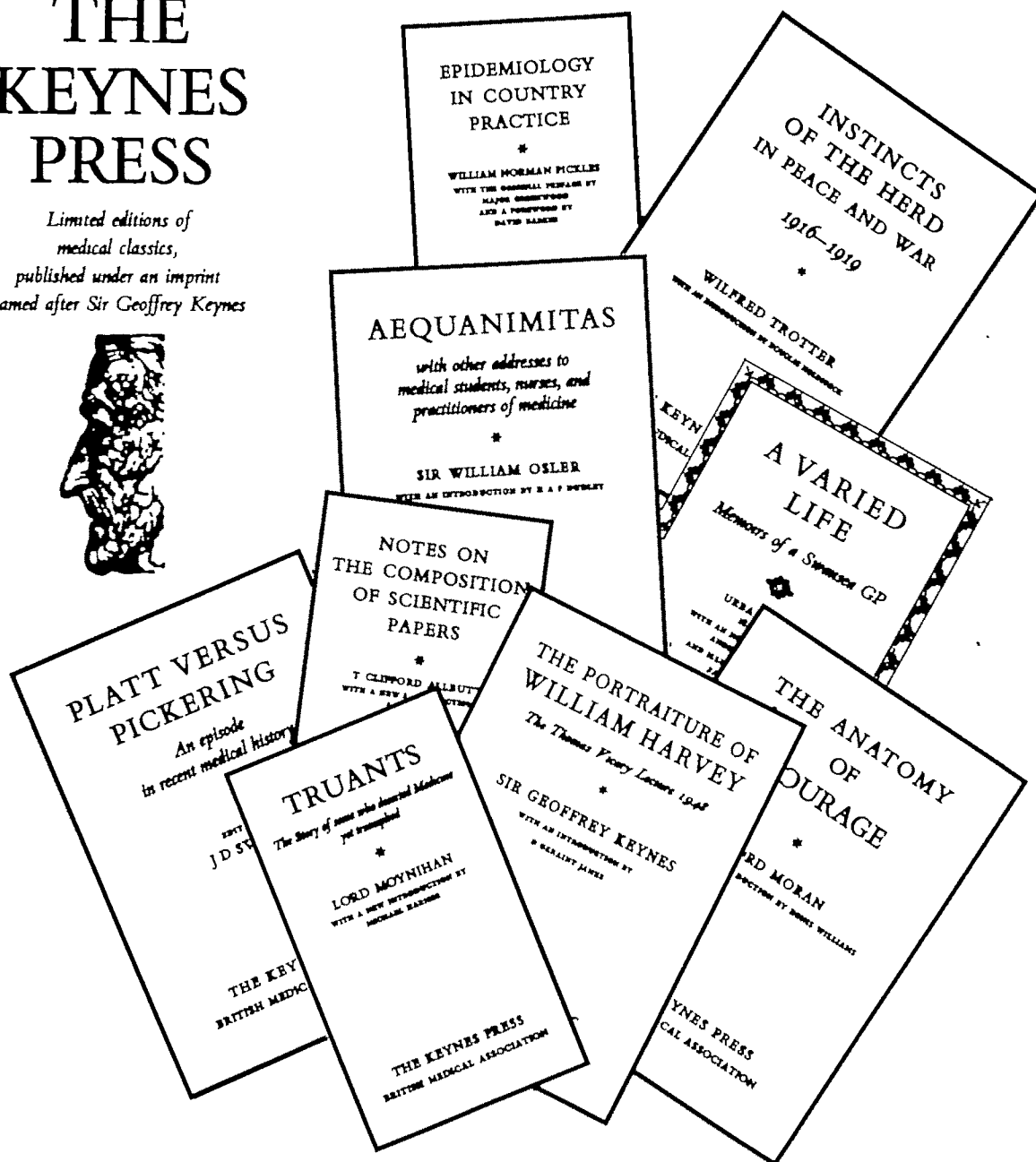
Both these awards are available to medical graduates and non-medical scientists resident in the United Kingdom or Eire. They may be held concurrently with other awards. A curriculum vitae should be sent with information on the applicant's research project and details of proposed visit (preferably with confirmation from the centre(s) visited) to: Dr S. Nagasubramanian, Glaucoma Group Secretary, Glaucoma Unit, Moorfields Eye Hospital, High Holborn, London WC1V 7AN. The closing date for applications is 14 June 1986. The successful candidate will be informed by August 1986.

Asia Pacific Academy of Ophthalmology

The 11th Congress of the Asia Pacific Academy of Ophthalmology will be held in Kuala Lumpur on 24–28 May 1987. The deadline for abstracts is 31 December 1986. Further information from Dr Keshmahinder Singh, Malaysian Ophthalmological Society, 124 Jalan Pahang, 53000 Kuala Lumpur, Malaysia.

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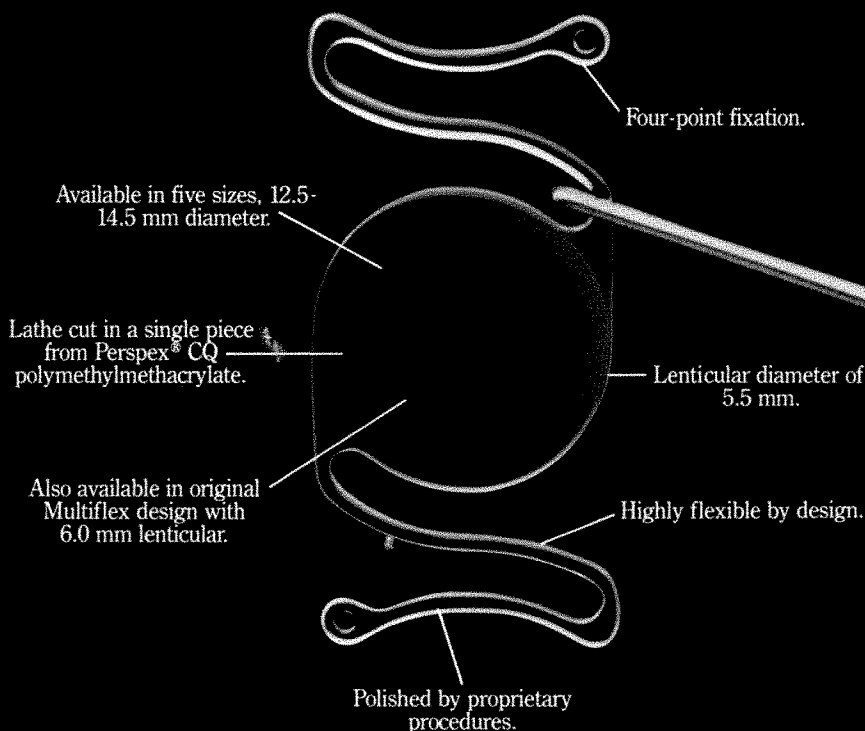
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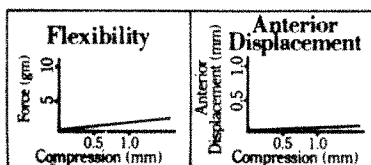
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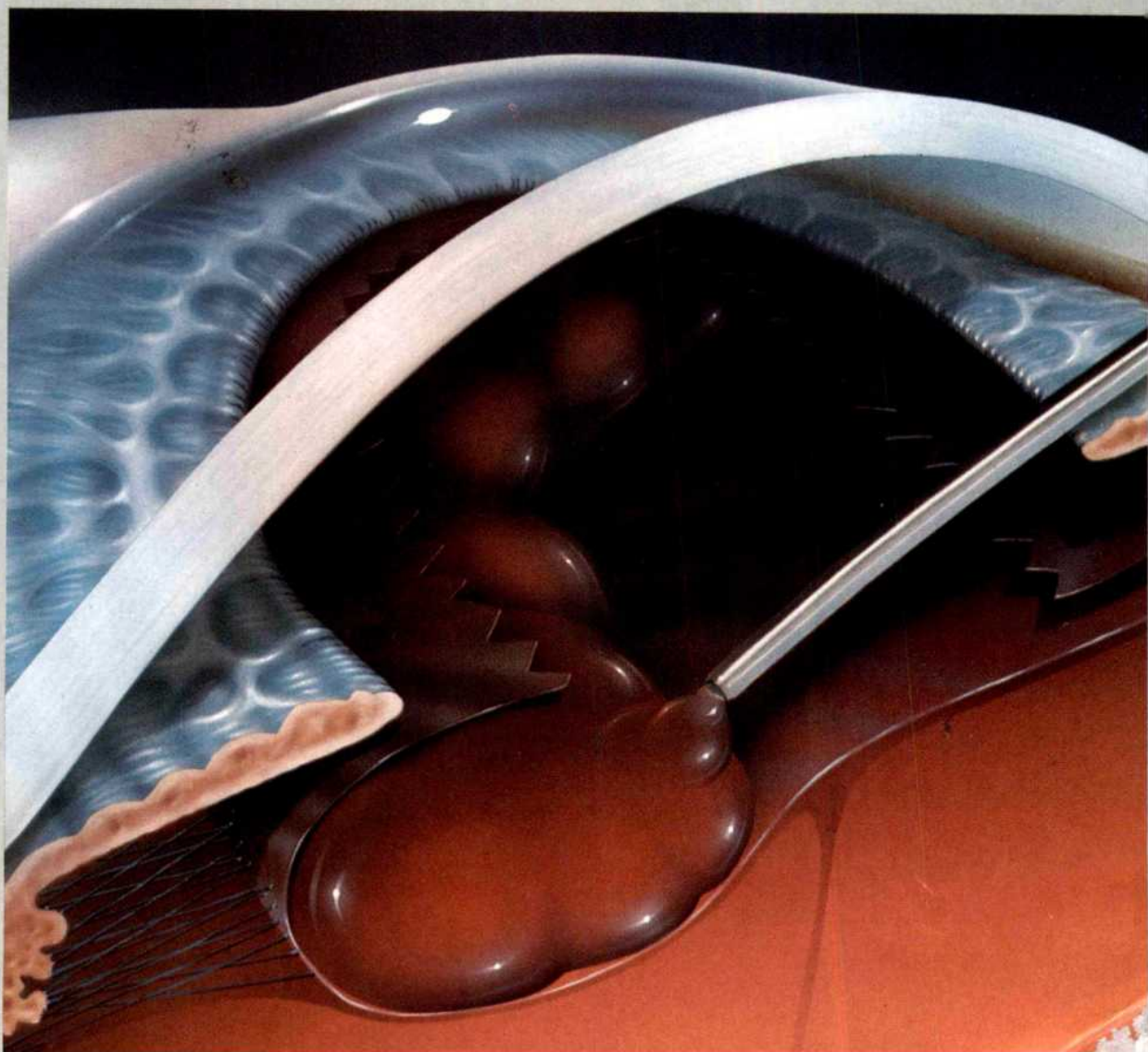
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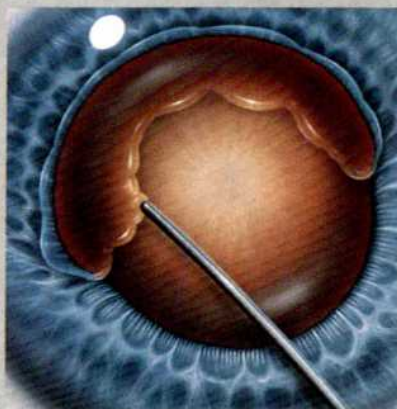


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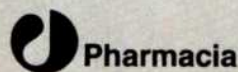
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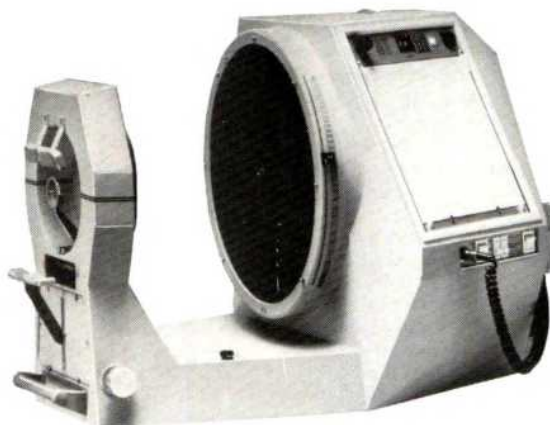
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I. Cataract surgery: interim results and evaluation of a randomised controlled trial

OXFORD CATARACT TREATMENT AND EVALUATION TEAM (OCTET)*

SUMMARY A randomised controlled trial in progress for more than five years, with no loss to follow-up (except death), assessed 333 eyes treated by three methods of cataract surgery. They were (A) intracapsular extraction and contact lens usage, (B) intracapsular extraction and implantation of an iris supported lens (Federov I), and (C) extracapsular extraction and implantation of an iridocapsular lens (Binkhorst 2-loop). The purpose of the paper is to report interim visual results, complications, and corneal endothelial cell loss. More eyes in groups A (contact lens) and C (extracapsular+implant) achieved better visual acuity than in group B (intracapsular+Federov lens), which also had more postoperative complications. Both implant groups lost more endothelial cells than the non-implant group, which did not differ significantly from group B before one year.

A randomised controlled clinical trial on cataract surgery was started in 1980 at a time when there was general uncertainty whether intracapsular or extracapsular extraction was the better method for removing cataracts and whether the potential risks of lens implantation would outweigh the benefits, since contact lenses can be used as an alternative in the correction of aphakia.¹

The practice at the time was strongly influenced by the published works of Binkhorst, and the most widely used intraocular lenses were iris supported.² As it is clearly impracticable to have too many randomisation categories in a clinical trial of this

nature, it was possible to test only one style of implant in each category of treatment, and the lenses chosen were the Binkhorst 2-loop iridocapsular lens for extracapsular extraction and a modified Binkhorst 4-loop lens for intracapsular extraction (the Federov I lens). The Federov I lens was chosen because the participating surgeons were already familiar with this lens and had used it for more than five years³ and because it was widely used in the United Kingdom at the time. The Shearing type of posterior chamber lens was not yet widely known.

It was appropriate to compare lens implantation with conventional intracapsular surgery and the use of contact lenses, which would eliminate the optical disadvantages of aphakic spectacles. If contact lenses could be fitted and tolerated universally, there would scarcely be a need for lens implantation. The choice of the type of contact lens, however, need not be restricted, since they can be and are freely exchanged, provided the best techniques and material are available to the patients in the study.

Although a reversal of trends has occurred in relation to the number of iris supported and posterior chamber lenses used,⁴ the latter is by no means trouble free.⁵ There are many patients fitted with iris supported lenses who still require careful management based on sound facts. Furthermore, there are remarkably few well documented reports of the long term follow-up of intraocular lenses in general. So far all reports with a minimum follow-up period of five

* PARTICIPANTS: Principal investigators: H Cheng, K McPherson,¹ A J Bron. Contributing surgeons: H Cheng, D Boase, G Bell. Anaesthetist: R Fordham. Research fellows: N Price, P Jacobs, M Noble, S MacLennan, A K Bates. Consultant in contact lenses: J Kersley.² Independent review committee: A R Elkington,³ M Ruben,⁴ J Mann,¹ A Ridgway.⁵ Computer programmer: L Jones. Photographer: D Barbour. Contact lens practitioner: D White. Opticians (optometrists): U O'Beirn, C Lydon. Nurse technician: A Ambrose. Trial administrators: M Platts, K Smith. TRIAL LOCATION: The Eye Hospital, Oxford.

¹Department of Community Medicine and General Practice, Oxford University, Oxford.

²Harley Street, London.

³Department of Ophthalmology, Southampton University.

⁴Moorfields Eye Hospital, London.

⁵Manchester Royal Infirmary, Manchester.

Correspondence to Mr H Cheng, FRCS, The Eye Hospital, Walton Street, Oxford OX2 6AN.

the late arrival of science

considered more important to pursue than all others and for the ultimate benefit of us all.

The Oxford team, therefore, are to be congratulated for their integrity and persistence, and we can welcome the news that the clinical decisions made over the changing years can now be regarded as scientifically correct and appropriate. The fact that the three surgical methods compared in their trial have now all been widely abandoned makes little difference to the value of the results achieved. The surgical steps tested here are ones made by many of us as practising surgeons, and it is comforting to know that our decisions made then on grounds of instinct or personal persuasion were sound. It is reasonable to assume, as the authors suggest, that further decisions made later, particularly concerning the now widespread use of intraocular lenses supported entirely within the posterior chamber, will be equally valid.

Similarly, the rigid control of this trial has precluded not only the newer styles of implant lenses and fixation methods but also the use of viscoelastic fluids used to protect the corneal endothelium. These fluids have done much to reduce the cell loss previously associated with modern methods of extracapsular extraction and highlighted in this paper.

The factors which make this trial so useful, randomisation, the inclusion of a control group, no loss of follow-up, and separate teams for patient management and assessment of results, require determination to pursue, maintain, and administer. Sadly, it is unlikely that this report will herald a new era, for the same reasons. Public opinion has now been so well manipulated by indirect advertising in the lay press that the chances of finding a sizable population of patients willing to undergo control surgery rather than have the 'benefit' of the latest developments are remote. Had the early advocates of intraocular lenses adopted such criteria and methods when the climate for such investigations was more favourable, their cause might have been advanced sooner than was the case.

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the fact that the Oxford team have been inclined to series—large and small—some of which do no more than reflect the manual dexterity or honesty of the surgical reporter. Such accounts are of little benefit to other surgeons and can seldom be applied meaningfully to other groups of patients, even when they are nationally collated.

The use of scientific method for the investigation into the place of a new form of treatment requires at least (1) a prospective study; (2) randomised selection of similar patients for the various forms of treatment to be compared; (3) no loss to follow-up for the duration of the study and no exclusion from the trial of patients already admitted and who had correctly met the original criteria for entry; (4) separate treatment and evaluation teams of clinicians; and (5) rigid adherence to the original protocol.

The requirement for an investigation to be blind is almost impossible to achieve in a study of surgical method.

In their study the OCTET have met all the possible requirements. Informed patients were randomly allocated to three different forms of cataract management, each perfectly valid at the time of the start of the programme. Popular opinion and fashion in treatment techniques for cataract and lens style changed dramatically during the course of the study, but the principles above were appropriately con-

years are of iris supported lenses,⁶ and only one has no loss of patients to follow-up.⁷

The authors believe that this is the first randomised controlled trial to be reported, and, though the modes of treatment tested are no longer popular, the results of the study would still be useful and should provide both valid data to help formulate opinions and background information to test future claims.

The purpose of this paper is to report on: (1) interim visual acuity, (2) complication rates, (3) corneal endothelial cell loss.

Patients and methods

The patients were recruited from a pool of cases requiring surgery, the need for which is based on visual criteria. All eligible patients were given a detailed written account of the choices of treatment. They were interviewed and given explanations, usually in the presence of a relative, and signed informed consent was obtained. Their age range was from 55–90 (Table 1). Exclusion criteria aimed to eliminate patients with other ocular diseases likely to

affect visual outcome and to ensure inclusion only of those patients with uncomplicated senile cataract. Patients had also to be suitable and willing to wear a contact lens (CL) (Table 2).

To be eligible to contribute patients to the study the surgeon must be familiar with both intra- and extracapsular techniques; must have carried out at least 300 cataract operations, which must include a minimum of 25 lens implantations; and must abide by the protocol.

Those who took part were in fact much more experienced. Surgeon I had been doing lens implant surgery since 1973 and had used extracapsular surgery for two years before the study began.

RANDOMISATION

Three randomisation categories were used: group (A) intracapsular extraction and contact lens (CL); group (B) intracapsular extraction (IC) and 4-loop iris supported Federov lens; group (C) extracapsular extraction (EC) and 2-loop Binkhorst iridocapsular lens.

Each contributing surgeon had his cases randomised separately, and it was permitted to randomise the second eye in the study if the first eye of that patient had been assigned a contact lens.

Table 1 Age range of patients

No of patients	Age range in years
23	55–59
33	60–64
64	65–69
98	70–74
74	75–79
40	80–84
11	85–89

Table 2 Exclusion criteria

General categories	Specific categories
1 Corneal disease	e.g., Fuchs's dystrophy, cornea guttata >10 dimples, scarring, old herpes
2 Open-angle glaucoma	<2.5 mm
3 Shallow anterior chamber	Presence or history of
4 Iritis	Presence of proliferative
5 Juvenile onset diabetes mellitus	retinopathy in either eye or of moderate background retinopathy in fellow eye
6 Axial myopia >6.0 DS	
7 Previous retinal disease	e.g., Vein occlusion, retinal detachment, degenerative disease, known macular degeneration
8 Mobility problems affecting hands	e.g., Parkinsonism, stroke, severe arthritis
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Lens implantation was carried out only when an air bubble could be maintained in the anterior chamber, and the procedure was abandoned if there was vitreous loss. Preoperative medication included the use of intravenous mannitol for all patients destined

for an implant who were less than 70 years old and had no contraindications to its use. All but two patients had general anaesthesia, which was of a uniform technique⁸ with halothane and assisted respiration.

The patients were seen daily for five days or until their discharge, but scheduled postoperative assessments were made at 48 hours, the fifth day, one month, six months, and thereafter at each anniversary of surgery. The clinical assessment was made by research registrar trained in ophthalmic observations. The visual acuity was assessed independently by a trained optician (optometrist) who had no professed bias towards either mode of treatment. Masking procedures were used in endothelial cell counting, in reading fluorescein angiograms, and where possible in reading the end point of corneal thickness measurements. Masking was attempted in refraction, but in practice it was difficult and not always practicable to do this for large numbers of patients. However, the assessment of corrected visual acuity was carried out by a forced choice method as defined in the manual and was used throughout the study. The method was similar to the one used in the Diabetic Retinopathy Study.⁹

An experienced contact lens practitioner fitted all contact lenses at six weeks to two months, and related complications were seen by a visiting consultant in contact lenses. A nurse practitioner, herself a CL wearer, helped patients manage their CL and had a telephone which enabled patients to contact her directly. Uncomplicated cases with daily-wear hard lenses were seen as often as necessary until tolerance was established. Thereafter, they were seen at the scheduled visits. Soft daily-wear and extended-wear lenses were checked as often as needed until a quiet stage was reached, and thereafter at three-monthly intervals for extended-wear cases.

COMPLICATIONS

Based on the experience of a Pilot Study¹ 27 known events or complications were listed which required either additional hospital visits or treatment. In general, postoperative complications were defined as follows if they did not conform to those listed in Table 5: as an event (1) needing additional surgical intervention, or (2) related to the surgery and reducing the visual acuity by two lines of the Snellen chart to 6/12 (20/40), or (3) requiring prolonged additional medication.

Additional events were recorded on these criteria. All patients suffering a drop in acuity to 6/12 (20/40) or by two lines of Snellen with no obvious cause had fluorescein angiography performed, which was read independently. Cystoid macular oedema (CMO) was recorded only if it was proved angiographically.

ENDOTHELIAL CELL COUNTS

Corneal endothelial cells were photographed with a Nikon non-contact specular microscope and counts derived by grid counting. The method has been described¹⁰ and its precision estimated.¹¹ Cell densities were estimated before surgery, at one month, six months, and yearly after operation. Masking procedures were used for counting.

Results

Three hundred and twenty-seven patients and 333 eyes were recruited from 15th January 1980 to 31 June 1983. The number of patients asked initially was not known, but 400 patients were formally approached and 67 elected to have lens implants. Six patients allowed both eyes to be randomised for the trial. The mean age of patients was 72 years with a range as shown in Table 1. The numbers in each group are shown in Table 3.

DEATH AND LOSS TO FOLLOW-UP

One year from the beginning of the study two patients each from groups A and B had died, but by the three-year stage the number dead had increased to 21 (A=6, B=7, C=8). However, apart from death there was no loss to follow-up.

RANDOMISATION

The numbers of patients treated by each surgeon in the three treatment groups are shown in Table 3. There was one deviation from protocol regarding the randomisation. In one case surgeon III changed from EC to IC extraction because the pupil would not dilate sufficiently to permit him to use his technique.

OPERATIVE COMPLICATIONS

The intraoperative complications are listed in Table 4. Surgeon III contributed only 17 cases in the last year of the study, and all his cases were entered within his first six months of joining.

Vitreous loss was the most serious complication and occurred more frequently in EC than in IC surgery. Capsule rupture occurred more frequently during routine intracapsular surgery than when it was combined with lens implantation. In no case where ruptured capsule had occurred was residual lens

Table 3 Number of eyes and patients by treatment groups

Groups	No of eyes	No of patients
A	111	109
B	110	110
C	112	112

Four patients have CL in one eye and an implant in the other. Some patients in Group A are also in groups B and C.

Table 4 Complications during surgery arranged by surgeon

Complication	Surgeon I (n=274)			Surgeon II (n=42)			Surgeon III (n=17)		
	n=56			n=218			n=42		
	1st 6 months			After 6 months					
	A	B	C	A	B	C	A	B	C
Ruptured capsule	2			4	2		1		1
Vitreous loss		1	4	2		1	1	2	2
Hyphaema		1		4	2		2	1	2
Torn iris			1	1	3				
Others*		1		1	1				

*Others=one local anaesthesia used (A), one torn Descemet's membrane (B); one misplaced inferior loop (B).
n=number of eyes.

Group A=IC, B=C+Federov I lens, C=EC+Binkhorst iridocapsular lens

Table 5 Failure of implantation

Surgeon	Total no patients	Group	Vitreous loss	Bulgy vitreous face	Torn iris	Ruptured vitreous face but no vitreous loss
1	274	B		5	1	1
		C	5	1	-	-
2	42	B	2	-	-	-
		C	2	-	-	-
3	17	B	-	1	-	-
		C	-	-	-	-

matter sufficient to interfere with vision. Approximately 30% of cases of IC extraction (group A) had no α -chymotrypsin, but only one of these patients suffered a ruptured capsule.

There were nine and six cases respectively in groups B and C where implantation was abandoned, either because of vitreous loss or to avoid serious complications (Table 5); but these cases remained in their randomisation categories for the consideration of postoperative complications and visual results.

POSTOPERATIVE COMPLICATIONS

The postoperative events or complications are listed in Table 6. Treatment groups are arranged according to initial randomisation, and all cases were included in this assessment. Cases with raised pressure ≥ 26 mmHg are listed in Table 7. Significantly, more eyes in group B had raised intraocular pressure than in Group C ($p<0.001$). There were significantly more eyes with raised pressure following the use of α -chymotrypsin, but its use was not associated with high pressures at 48 hours, the fifth day, or subsequently. 'Hypopyon' included all cases with the

Table 6 Postoperative complications and events

Complications or events	Groups					
	A		B		C	
	1Yr	AGG 1Yr	1Yr	AGG 1Yr	1Yr	AGG
Raised pressure	18	19	37	38	16	16
CMO	9	10	20	24(23)	14	16
Capsule opacity					4	19
Suture removal	12(10)	15(13)	11	13	17	19
Uveitis (severe)	2	3	12	13	7(6)	7(6)
Subluxed implant			8(5)	10(5)	3	3
Shallow anterior chamber	1	1	9	9	1	1
Hypopyon	2	2	7	8(7)	2	3
Hyphaema	7	7	5	5	4(3)	6(4)
Blepharitis	2	10	1	3	1	3
Cornal abrasion	3	7(5)	0	1	0	4(3)
Cornal abscess	3	6	1	1	0	2(1)
Marginal keratitis	2	6(4)				
Bullous keratopathy			0	3	0	4
Conjunctival bleb	3	3	1	1		
Vitreous to section	3	3				
Excess remaining lens matter					3	3
Excess deposits on implant			3	3		
Dislocated implant			2	3		
Ven occlusion	1	3	0	1	1	1
Retinal detachment	1	1	0	2	2	2
Suture reaction			1	2	2	2
Pupal block glaucoma			2	2	2	2
Cornal oedema	1	1	0	0	2	0
Episcleritis prolonged	2	2	2(1)	2(1)		
Implant removal and anterior vitrectomy			2	2		
Choroidal effusion					1	1
Iris in wound	1	1				
Endophthalmitis	1	1				
Infected corneal ulcer	0	1				
Displaced pupil	1	1				
Choroiditis	1	1	1	1		
Repositioning of implant			1	1		
Tear in Descemet's membrane			1	1		
Intracapsular implant/endothelial touch			1	1		
Traumatic rupture of section and implant extrusion			1	1		
Low-tension glaucoma			1	1		
Vitreous opacities					0	1
Iris cyst					1	1

Group A=intracapsular extraction+CL, B=intracapsular extraction+Federov I lens, C=extracapsular extraction+Binkhorst iridocapsular lens. AGG=aggregate episodes for five years. Where an eye had more than one episode of a complication the number of eyes affected are shown in parentheses.

morphological appearance of a hypopyon without any distinction being made between an infection and a fibrin clot. All such cases were treated for infection for 24 hours and a clinical decision made as to whether an infection had occurred. In only two cases when the 'hypopyon' occurred in the immediate

Table 7 Time course of 'raised pressure' complication*

	Number of eyes by group		
	A	B	C
0-48 h	8	13	2
48 h-1 wk	2	2	0
1 wk-1 month	6	20	8
1 month-12 months	1	2	5
Later than 12 months	2	1	1
Cumulative total	19	38	16

*IOP >26 mmHg or lower IOP deemed clinically to require treatment.

postoperative period, in groups B and C respectively, was there pain, and in no case was there an eventual drop in visual acuity to less than 6/9 (20/30).

Subluxation of the implant occurred more frequently in the IC group, and all cases recorded as having this complication have suffered displacement of one loop. Five cases were rectified surgically, eight cases by positioning the patient and by the use of drops. One eye suffered four subluxations before the implant was fixed by a McCannel suture. In only one other instance had subluxation occurred twice in the same eye.

The depth of the anterior chamber was measured at regular intervals and recorded as shallow if it was less than 2.4 mm. In four cases such shallowing occurred within 48 hours, and immediate surgical intervention to reform the anterior chamber was required. The others either had no lens inserted or no corneal touch, and no surgery was needed in these cases.

'Corneal oedema' indicates the presence of oedema within the limbal wound. More than one case of bullous keratopathy occurred in each of the implant categories but not until two years after surgery.

Angiographically proved cystoid macular oedema appeared twice as frequently in group B as in group A and much more frequently than in group C, but the difference is not statistically significant. Interestingly, of the 14 cases in group C with CMO, all but two had intact posterior capsules. For groups B and C, CMO was not related to subluxation, but there was a significant association between CMO and uveitis ($p < 0.004$).

Suture reaction was recorded if the patient sought advice at an unscheduled visit or if the suture needed to be removed either because of excessive reaction or because of astigmatism. The former virtually disappeared after 10-0 monofilament sutures were used, and 16 eyes, almost equally distributed between the groups, had sutures removed because of astigmatism greater than 4 dioptres.

That there were more hyphaemata after one year in group C is surprising, but one eye had two microscopic hyphaemata of no definite cause, probably owing to sphincter erosion.

Corneal abrasion and abscess formation occurring in group C (EC with implant) were contact lens problems in eyes which failed to receive an implant because of intraoperative complications.

The complications which were unresolved at one year are listed in Table 8.

ENDOTHELIAL CELL DENSITIES

Endothelial cell counts of the operated eyes were not available for the first 16 patients who entered the study. Subsequently all had endothelial cell photographs taken. The mean cell densities of the three treatment groups were similar before surgery. One month postoperatively cell loss was significantly greater in the EC group, though the overall amount of cell loss was acceptable and the values were not too different from those published in the current literature.¹⁵ Cell loss increased with time up to one

Table 8 Unresolved or unresolvable complications at one year

	No. of eyes by treatment groups		
	A	B	C
	Unresolved Not resolvable	Unresolved Not resolvable	Unresolved Not resolvable
Glaucoma	1	11	5
Shallow anterior chamber	1	1	
Uveitis		3	
Subluxed implant		2	
Corneal oedema	1		
Vein occlusion		1	
Capsule opacity			2
Cystoid macular oedema	4	5	3
Blepharitis	2	1	1
Diplopia		1	1

Table 9 Endothelial cell loss: percentage loss in each group up to one year

Treatment group	1 Month	6 Months	1 Year
A Mean	10.7	12.1	15.1
SD	16.4	13.5	14.0
n=	74	83	78
B Mean	10.9	14.1	20.1
SD	12.4	13.1	16.9
n=	75	83	78
C Mean	16.3	18.7	23.3
SD	16.3	15.5	11.8
n=	74	88	86
Results of variance analysis			
A v B	NS	NS	p<0.06
B v C	p<0.05	p<0.05	NS
A v C	p<0.05	p<0.01	p<0.001
Overall integrity	p<0.05	p<0.01	p<0.01

n=Number of eyes NS=not significant

year, and at each time point the amount of cell loss tended to be greater for group C than for the other two groups. Variance analysis of the results of the three groups showed a significant difference at each of the three time points (Table 9). Only the patients of surgeon I were included to reduce potential variables in surgical techniques and because he contributed more cases than the other two combined. The overall results suggest that both implant groups lost more cells than the non-implant group, and,

though the IC group with implant did slightly better than the EC group in the early stages, there was no significant difference between the two implant groups at one year. These results were not altered by the inclusion of cases from surgeons II and III.

VISUAL ACUITY

The visual acuities at one month (Fig. 1) and at one year (Fig. 2) are grouped according to levels of vision in Table 10. At the one-month stage the acuities for group A were obtained by spectacle correction, but the one-year acuities were obtained by a combination of contact lenses and additional spectacle correction. More eyes achieved 6/9 (20/30) acuity or better in group A than in the others at one month, but this trend was reversed at one year (Table 10). Ninety-seven patients in group A were still wearing CL at the end of one year (44 daily wear and 53 extended wear). Twenty-three patients had 6/18 (20/60) acuity or less at the one-year stage. The causes of poor visual acuity and the postoperative complications are listed in Table 11.

Discussion

The study design would have been improved if a fourth arm of EC extraction without implant could have been introduced into the randomisation. This was not considered ethical, as it was not a current

Number of eyes

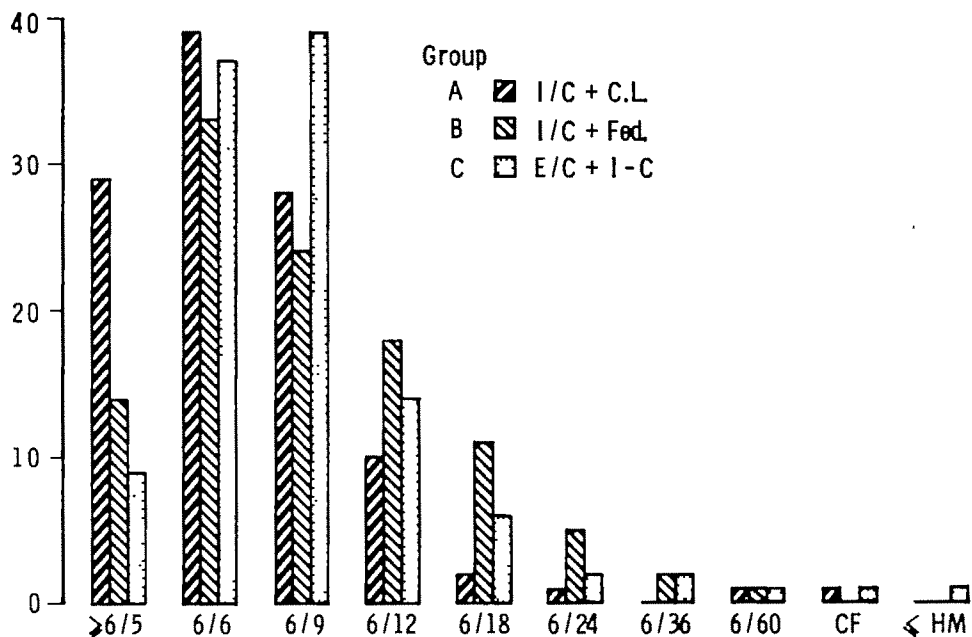


Fig. 1 Corrected distance visual acuity at one month postoperatively by treatment groups

Number of eyes

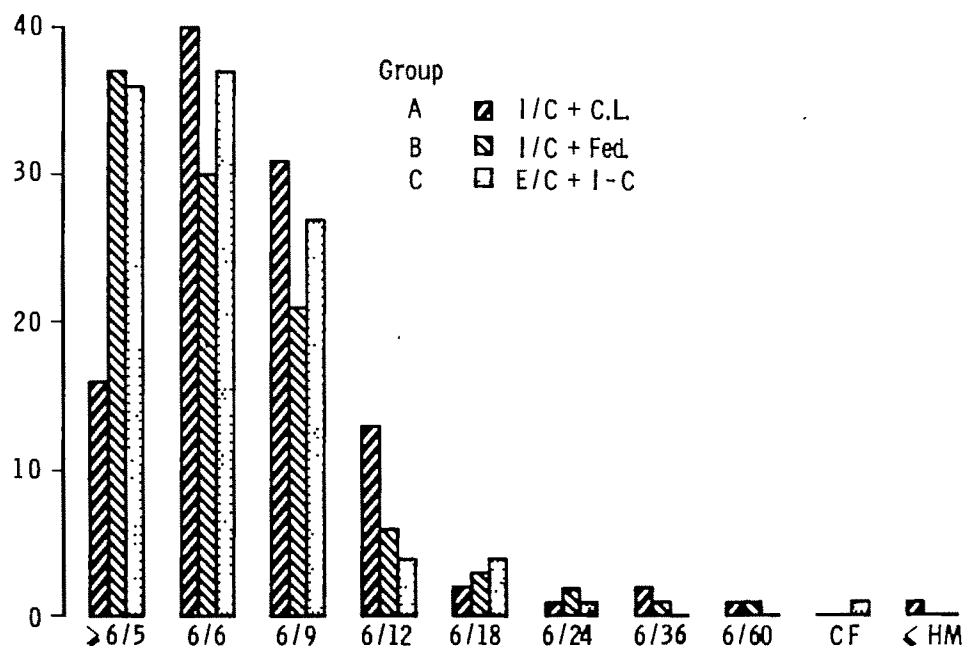


Fig 2 Corrected distance visual acuity at one year postoperatively by treatment groups

mode of treatment at the time of inception of the study. A weakness of the study is that there is no allowance for incorporating innovations which may be considered improvements in treatment. A strength is the standardised conditions, which were maintained more or less constant throughout the study. Critics of the Federov I implant used in conjunction with IC extraction argued that the anterior loops can cause intermittent corneal touch, but a study using high-speed cinefilm did not confirm this impression in cases without complications.¹² Results of interim reviews monitored by an inde-

pendent committee and conducted at six-monthly intervals did not show differences between groups that were significantly great to warrant a change in the structure of the study, and recruitment was completed as planned.

Surgeons II and III contributed comparatively few cases, so that their intraoperative complications may not be representative. Surgeon I's contributions form the bulk of the study, so an analysis of his intraoperative data is more meaningful. Among his patients vitreous loss was the major complication and occurred more frequently in EC extraction and the

Table 10 Number of eyes with different levels of corrected VA (%)

Treatment group	No. of eyes	Snellen acuity		
		≥6/6 (20/20)	≥6/9 (20/30)	≥6/12 (20/40)
<i>1 Month</i>				
A	109	66 (60)	93 (85)	103 (94)
B	107	47 (44)	70 (65)	88 (82)
C	111	46 (41)	84 (75)	98 (88)
<i>1 Year</i>				
A	107	54 (50)	93 (87)	103 (96)
B	101	56 (55)	79 (78)	85 (84)
C	110	73 (66)	99 (90)	103 (94)

>= Equal to or better

Table 11 Eyes with VA <6/12 and associated complication

Corrected VA							Complication	Total eyes
6/18	6/24	6/36	6/60	CF	PL			
B	A		B	C			Mac deg	4
A	C	B					CMO	7
C							Ret detachment	2
					A		Glaucoma	1
B							Uveitis	1
		C					??Subluxed implant	1
C							Vein occlusion	1
B	A		A				Unknown	5
							Total	22

Each letter indicating one case of that treatment group (group A=8, B=6, C=8)

first six months of the study. Although he had been using EC extraction routinely for two years, it is still possible that in the first six months his surgical techniques and operating condition had not yet been perfected. These factors may have accounted for the higher rate of complications than later on. A review of the surgical notes showed that all cases of vitreous loss in group C occurred while cortical lens matter was being removed and before the stage of lens implantation had been reached.

The most numerous postoperative complications were raised pressure and cystoid macular oedema. An arbitrary level of pressure was selected, and any eye with a pressure of 26 mmHg or greater was considered to have raised pressure, which occurred more frequently in group B than in groups A and C ($p < 0.001$). In group B α -chymotrypsin was used routinely to facilitate delivery of the cataract because the pupil was often poorly dilated. Only Mydrilate (cyclopentolate 1%) was used to enlarge the pupil so that the iris could remain responsive to intracameral Miochol (acetylcholine 1% and mannitol 3%) during surgery. A small pupil was thus obtained to maintain the iris supported implants in the correct position. However, even allowing for the fact that only 70% of eyes in group A had received α -chymotrypsin, the proportion of eyes developing raised pressure in group B was still higher than in group A. Significantly, more eyes developed raised pressure if α -chymotrypsin was used, but there was no correlation between the use of α -chymotrypsin and the level of the rise in pressure. In all cases the pressures were controlled or settled spontaneously by the six-month stage.

By doing fluorescein angiography only when there is a reduction of vision, our method of assessment would detect only clinical CMO. This complication occurred in group B (IC+implant) more commonly than in the other two groups, but the difference is not statistically significant. In groups A, B, and C there were only two, three, and one cases respectively which remained unresolved by the one-year stage. Interestingly, all but two of the 14 cases with CMO in group C had intact capsules, which clearly are not always an effective protection against this complication.

Nine eyes with implants were noted to have some shallowing of the anterior chamber, and eight of them occurred in group B. In half of the eyes the cause was not known with certainty, but in half the shallowing was due to displacement (without subluxation) of the implant. Although the majority resolved spontaneously, that this should occur so frequently in group B is a worrying feature of this type of implant.

Some complications occurred more than once in

the same eye, and Table 6 distinguishes between episodes recorded and the number of eyes affected. Fortunately the number of eyes developing the same complication more than once is limited.

Some complications are not expected in the first year, and thus no case of bullous keratopathy was recorded until after the two-year stage was reached. Likewise only four cases had capsule opacities affecting visual acuity, but the aggregate total was 19 by the time the study had been in progress for 4.5 years.

If serious complications are considered, there was no significant difference between groups except for raised pressure, because of small numbers; but, as regards the number of all the complications, group B had far more than group A or C.

If a grading system¹⁰ was used to assign a numerical score for each complication, more points being awarded the more serious the event, group B scored significantly higher than either group C or A. Thus either by looking at the frequency of occurrence of complications or by the use of a grading system group B seemed to be doing less well than the other two groups.

From the point of view of visual acuity the difference between groups is not significant or great, but the trend suggests that, at the one-year stage, group C is doing better than either group B or group A.

Almost all the patients in group A had been fitted with a contact lens by the one-year stage, and the proportion of eyes achieving 6/9 (20/30) acuity or better had diminished in comparison with the one-month stage, when the visual acuities were obtained through spectacle correction (Table 10).

In our study of cell loss only central corneal densities were estimated, as the number of patients involved would make a study of morphology logistically impossible. At one month cell loss would reflect intraoperative factors. Although cell loss was significantly greater with the EC group, it was only 16.3%, and, with the mean loss of 10.7 and 10.9% respectively in the other groups, the results are within current claims,^{11,12} which suggests that the surgery has been competently carried out. It is, however, a little surprising that the loss in the IC group with a two-plane iris supported lens was significantly less than in the EC group, which suggests that it is technically possible to execute the manoeuvres of implanting an iris-supported lens without undue trauma. That the implant groups should lose significantly more cells subsequently is worrying, but it is comforting to find that by the one-year stage there is no significant difference between the IC groups with implant and the EC group.

Many variables may affect cell loss, and a more

detailed discussion will be presented in a separate report on cell loss after a longer follow-up, which is clearly necessary to determine whether increased loss with time is clinically important.

Cell loss apart, the evidence thus far, from the complication and visual acuity data, suggests that lens implantation with extracapsular extraction compares favourably with intracapsular extraction and the use of a contact lens. However, significantly more complications occurred in eyes with iris supported lenses, amply confirming current opinion that such lenses should be avoided for new cases of lens implantation.

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II. Use of a grading system in the evaluation of complications in a randomised controlled trial on cataract surgery

OXFORD CATARACT TREATMENT AND EVALUATION TEAM (OCTET)*

SUMMARY A randomised controlled trial in progress for more than five years assessed 333 eyes by three methods of cataract surgery. These were (A) intracapsular extraction and contact lens usage; (B) intracapsular extraction and implantation of an iris supported lens (Federov I); and (C) extracapsular extraction and implantation of an iridocapsular lens (Binkhorst 2-loop). This paper reports the use of a weighting scale for rank scoring complications which are dissimilar or are mutually exclusive (for example, capsular versus contact lens problems) to allow the use of non-parametric statistics for comparing disparate features. Thus we found that group B did significantly worse in terms of the number and severity of postoperative complications, a trend in accordance with visual results. This method may serve as a useful model for similar studies.

The surgery of cataract extraction is linked to the manner of aphakic correction. For 30 years when spectacles were the treatment of choice the aim was to remove the entire cataract within its capsule. This certainty has disappeared with the advent of modern extracapsular surgery and intraocular lens implantation.

Hitherto intraocular lens surgery could be done either with intra- or extracapsular lens extraction, the choice depending on the style of intraocular lens that one believed would give the best results. Another

method of aphakic correction was by means of contact lenses which, when well tolerated, could give as good results as those produced by the use of intraocular lenses. What was in doubt was the method of cataract extraction and aphakic correction which would give the best visual results and the least complications.

To try to answer this question we started a randomised controlled trial in 1980 assigning eligible patients to one of three treatments current at that time: group (A) intracapsular extraction (IC) and contact lens; group (B) intracapsular extraction (IC) and iris-supported lens implant; and group (C) extracapsular extraction (EC) and iridocapsular lens implant.

The main aim of the study was to compare (i) visual outcome and (ii) complication rate.

When complications were being considered, comparison between groups was not possible in some instances, because some complications occurring in one group were not expected to occur in the others. Thus contact lens complications were not expected in the other two groups, nor were complications unique to implants, such as dislocation, expected in the contact lens group. Likewise capsulotomies would be expected after extracapsular but not intracapsular extractions. The fact that some of these complications differed in nature and seriousness presented the problem of making valid comparisons.

The purpose of this paper is to report the use of a

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grading system to allow widely differing events to be compared. The system has been applied to the assessment of complications occurring in the three treatment groups.

Material and methods

METHOD OF CLINICAL TRIAL

The method of the trial has been reported in detail.¹ It was fully developed in a 'manual of operations' which was approved by a peer review committee set up by the National Eye Institute.

METHOD OF DEVISING THE WEIGHTING SCALE

A list of all the complications was given to six independent observers, two of whom were ophthalmologists working in the United States. The others were from the United Kingdom and were involved with the study either as reviewers or assessors or were directly engaged in data collection.

Each was asked to grade the complications and assign a score of 1–3 according to seriousness. Grading was done by the following rules:

Grade I=Unlikely to need operation.

(Score 1) or unlikely to lead to a drop in visual acuity (VA) by two lines of Snellen chart or more.

Grade II=May need treatment.

(Score 2) or may lead to some loss of vision (by two lines or more) but not suddenly.

Grade III=Needs further treatment.

(Score 3) or needs emergency action; or leads to loss of VA by two lines or more; or leads to loss of VA by two lines or more if no emergency action is taken.

A numerical scale of 1–13 was obtained by adding the scores and subtracting 5 (Table 1). Although only three grades were used, the numerical scale gave a range of values to those events which have varying degrees of seriousness.

Results

Three hundred and thirty-three eyes in 327 patients were the subject of the trial. All eyes have been followed up for at least a year. Apart from death there was no loss to follow-up. There were 111 eyes in group A, 110 in group B, and 112 in group C. The age distribution of the patients has been reported,¹ and the mean age was 72 years.

Table 2 lists all the complications which occurred in the first year of follow-up for every patient as well as in the whole period of the study containing patients with different lengths of follow-up (one to five years). A more detailed description of the complications has been presented in a separate paper.¹ Table 3 shows the number of eyes suffering no complications and those that suffered one or more.

RESULTS OF THE SCORING BY MEANS OF THE WEIGHTING SCALE

There was surprisingly close agreement between observers in their scoring of the 39 events (Table 1). In only three instances (choroidal effusion, iris in wound, repositioning of implant) was there an overlap between the Serious (grade 3) and the Trivial (grade 1), where the scoring contained all three grades.

There was complete or 5/6 agreement in 20 events and 2/3 or better agreement in 30 events (Table 4).

Table 1 Grading of postoperative complications and events (arranged in alphabetical order)

Complication	Individual scores of six graders (A-F)						Score on derived scale
	A	B	C	D	E	F	
Blepharitis	1	1	1	1	1	1	1
Bullous keratopathy	3	3	3	3	3	3	13
Capsule opacities	2	2	3	3	3	3	11
Choroiditis	2	2	2	2	2	1	6
Choroidal effusion	2	3*	2	2	1	1	6
Conjunctival bleb	2	2	1	1	2	1	4
Corneal abrasion	1	2	1	1	1	1	2
Corneal abscess	2	3	3	2	3	3	11
Corneal oedema	3	2	2	3	3	2	10
Corneal ulcer (infected)	3	3	3	2	2	3	11
Cystoid macular oedema	2	2	3	3	3	3	11
Dislocated implant	3	3	3	3	3	3	13
Displaced pupil	2	1	1	2	2	1	4
Endophthalmitis	3	3	3	3	3	3	13
Epiaceleritis (prolonged)	2	2	1	1	2	2	5
Excess lens matter	2	2	2	1	1	1	4
Excess deposits on implant	2	2	2	1	1	1	4
Hyphaema	2	2	2	1	1	2	5
Hypopyon	2	3	3	3	3	3	12
Implant removal	3	3	3	3	3	3	13
Intermittent implant/endothelial touch	3	3	3	3	3	3	13
Iris cyst	2	1	1	1	1	1	2
Iris in wound	2	1	3*	2	2	2	7
Low tension glaucoma	2	2	2	2	2	2	7
Marginal keratitis	2	1	1	1	2	1	4
Positioning of implant	2	1	2	3*	2	2	7
Pupil block glaucoma	3	3	3	3	3	2	12
Raised intraocular pressure	2	3	2	2	2	2	8
Retinal detachment	3	3	3	3	3	3	13
Shallow anterior chamber	2	2	3	2	3	3	10
Subluxed implant	2	2	2	3	2	2	8
Suture reaction	1	2	2	1	1	1	3
Suture removal	1	1	1	1	1	1	1
Tear in Descemet's membrane	2	1	2	2	2	1	5
Traumatic extrusion of implant	3	3	3	3	3	3	13
Uveitis (severe)	2	2	2	1	1	2	5
Ven occlusion	3	2	3	3	3	3	12
Vitreous opacity	2	1	1	1	1	1	2
Vitreous to section	2	2	3	2	2	2	8

The scale is derived by adding all the scores and subtracting 5.

* Denotes overlap with grade 1

Table 2 Postoperative complications and events

Complications or events	Groups					
	A		B		C	
	1Yr	AGG	1Yr	AGG	1Yr	AGG
Raised pressure	18	19	37	38	16	16
Cystoid macular oedema	9	10	20	24(23)	14	16
Capsule opacity					4	19
Suture removal	12(10)	15(13)	11	13	17	19
Uveitis (severe)	2	3	12	13	7(6)	7(6)
Subluxed implant			8(5)	10(5)	3	3
Shallow anterior chamber	1	1	9	9	1	1
Hypopyon	2	2	7	8(7)	2	3
Hyphaema	7	7	5	5	4(3)	6(4)
Blepharitis	2	10	1	3	1	3
Corneal abrasion	3	7(5)	0	1	0	4(3)
Corneal abrasion	3	6	1	1	0	2(1)
Marginal keratitis	2	6(4)				
Bullous keratopathy			0	3	0	4
Conjunctival bleb	3	3	1	1		
Vitreous to section	3	3				
Excess remaining lens matter					3	3
Excess deposits on implant			3	3		
Dislocated implant			2	3		
Vein occlusion	1	3	0	1	1	1
Retinal detachment	1	1	0	2	2	2
Suture reaction			1	2	2	2
Pupil block glaucoma			2	2	2	2
Corneal oedema	1	1	0	0	2	0
Epusculitis prolonged	2	2	2(1)	2(1)		
Implant removal and anterior vitrectomy			2	2		
Choroidal effusion					1	1
Iris in wound	1	1				
Endophthalmitis	1	1				
Infected corneal ulcer	0	1				
Displaced pupil	1	1				
Choroiditis	1	1	1	1		
Positioning of implant			1	1		
Tear in Descemet's membrane			1	1		
Intracapsular implant/endothelial touch			1	1		
Traumatic rupture of section and implant extrusion			1	1		
Low-tension glaucoma			1	1		
Vitreous opacities					0	1
Iris cyst					1	1

AGG=Aggregate episodes for five years. Where an eye had more than one episode of a complication the number of eyes affected are shown in parentheses

Group A=intracapsular extraction+contact lens (IC+CL)
Group B=intracapsular extraction+Fedorov I implant (IC+Fed)
Group C=extracapsular extraction+indocapsular implant (EC+I-C)

Each eye in each treatment group was given a score according to the type and number of complications it suffered. This was done for the first year of each eye in the study and for the whole duration of the trial (one to five years).

Table 3 Number of eyes suffering more than one complication at the end of one year

Treatment group	Number of events or complications per case					
	0	1	2	3	4	5
A	56	37	12	5	0	1
B	36	33	25	11	4	1
C	53	42	10	5	1	1

Group A=IC+CL Group B=IC+Fed Group C=EC+I-C

Table 4 Agreement between observers for the 39 events

Level of agreement	No. of events scored
Complete	10
5/6	10
4/6	10
Half	6

Three events had an overlap between grades 3 and 1

The values were ranked and tested by non-parametric statistics. The Kruskal-Wallis test showed a highly significant variation between the three groups ($p<0.0003$) at one year. The Mann-Whitney U test showed that group B (IC+implant) was significantly worse than groups A (IC) and C (EC+implant), which did not differ significantly from A.

The same tests were applied to the aggregate total, and the relationship between groups was not significantly altered.

Discussion

Although there are limitations to comparing basically dissimilar entities (like apples and pears), there is often a need to make comparisons to arrive at clinical decisions. Cataract surgery is the commonest form of intraocular operation, and it has been estimated that more than 500 000 operations are carried out annually in the United States alone.² The use of intraocular lenses has increased steeply in the last decade, and it is important to know whether intraocular lens surgery is acceptably safe and how it compares with current alternatives.

For individual clinicians the choice of surgery is based on experience and belief. The logical process behind decision making is still based on a system of weighing up preferences and probabilities. The proposed weighting scale attempts to make the intuitive process more quantitative and thus more accessible to informed scrutiny.

That there was almost complete agreement between experienced ophthalmologists over grading what was trivial and serious gave such a system some

Table 5 Rank scores and comparison of treatment groups at 1 year Mann-Whitney U test

Groups tested	No. of cases	Mean rank	Z value (corrected for ties, 2-tailed p)
Group A vs Group B	111	96.17	-3.6111
Group B vs Group C	110	125.96	p<0.0003
Group A vs Group C	110	125.35	-3.3047
Group A vs Group B	112	92.89	p<0.001
Group A vs Group C	111	110.57	-0.353
Group B vs Group C	112	113.42	p<0.724

Group A=IC+CL Group B=IC+Fed Group C=EC+I-C

validity. That there was extremely good agreement between the observers in the United States and in the United Kingdom lent even more support to the adoption of this method. In only three instances (choroidal effusion, iris in wound, and positioning of implants, each affecting one case in the entire study) did one of the observers give each of them a score of three when all the other observers gave scores of two or one. It was surprising that, when the other events or complications were considered, more overlap did not occur, as many of the events must comprise problems which could vary greatly in severity.

A greater number of grades could have been used, but that would have introduced a different form of arbitrariness. It was comparatively easy to choose between serious, trivial, and intermediate grades, but it would be more difficult to be exact about the level of intermediacy. The derived scale gives intermediate values, which reflects the equivocal attitude of the ophthalmologists to some events that did not always have a serious outcome.

When this system was applied to our three treatment groups, group B scored considerably higher than either group A or C. This confirmed the

impression from the table of complications and events (Table 2) that intracapsular extraction with an iris supported lens was more prone to complications, which were additively more serious, than either intracapsular extraction with contact lens or extracapsular extraction with a lens implant. Furthermore, the outcome is in agreement with the results of assessment of visual acuity,¹ thus adding to the validity of the method, and it suggests that vision may be complication-dependent.

If we had applied this method of grading at an earlier stage, we should have obtained significant differences between groups. Such a system could have value in similar studies and will allow valid comparisons to be made even when numbers are small.

As many patients present with cataract in their sixth or seventh decade, a much longer follow-up will be needed to derive a true profile of all the problems which could arise in the three treatment groups. For example, would failure to tolerate a contact lens increase significantly with time, and would increasing numbers of eyes needing capsulotomy after extracapsular extraction lead to greater complications in group C? Our study will be able to answer some of these questions, and we believe our weighting scale will allow existing differences to be validly compared.

We thank Dr A R Hill for helpful conversation and Professors W J Stark and R C Drews for grading the complications.

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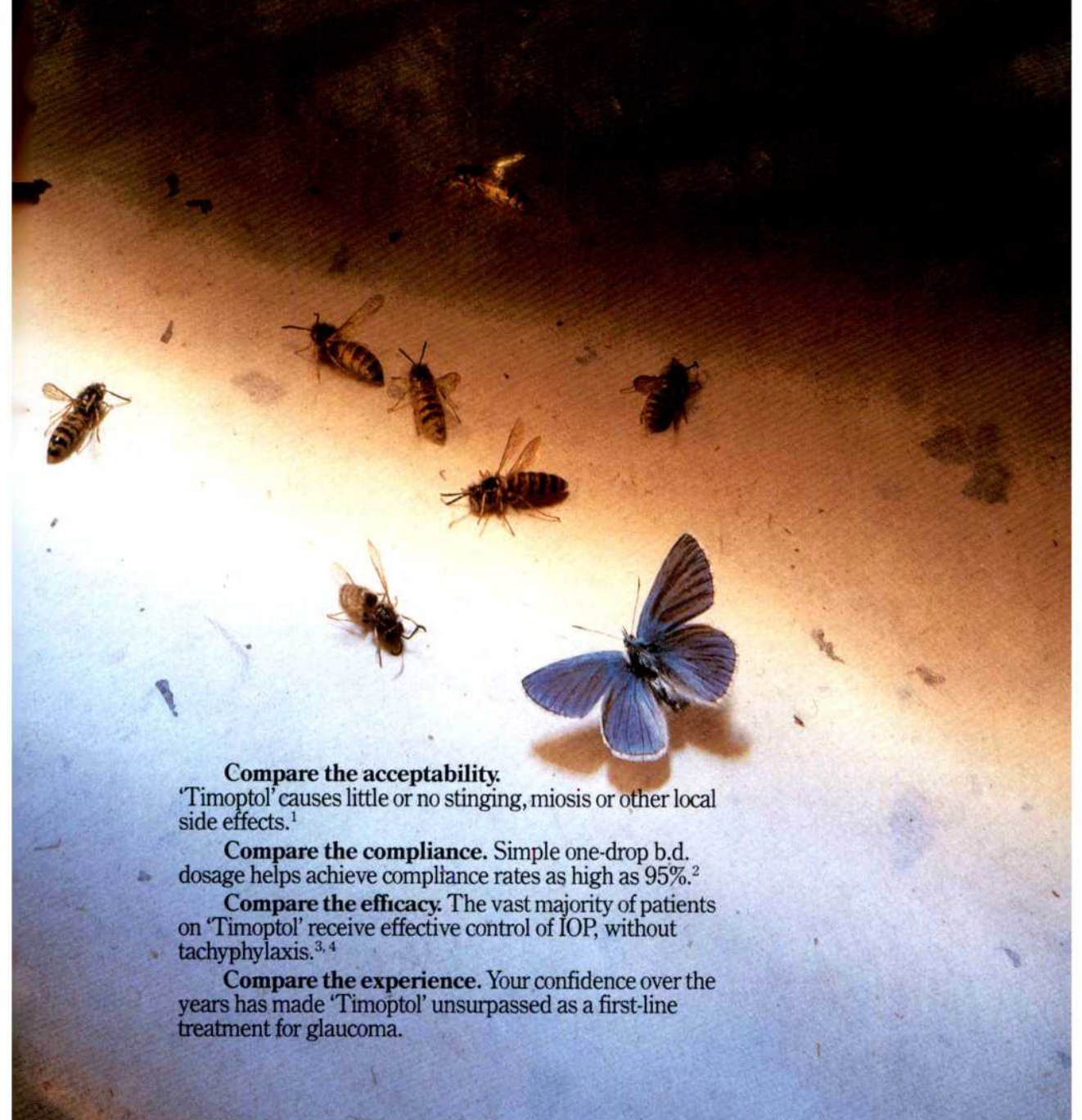
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Hypersensitivity, rash and urticaria.

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Retrospective comparison of lens implant surgery and cataract surgery in a provincial unit

J WATTS

From the Royal Victoria Hospital, Bournemouth

SUMMARY Evidence is presented which shows that the extracapsular cataract extraction technique combined with a Sinsky type posterior chamber implant is as safe a procedure as routine intracapsular surgery. Its results as reflected in the patient's satisfaction are superior.

This study was undertaken, firstly, to compare the results obtained by implant surgery with those obtained by routine cataract extraction, and, secondly to determine whether there was any difference in the success rate between the various implants available. In this relatively early period of implant surgery in the United Kingdom three major types of implant were available, and by chance each of three of the consultants in this unit began by favouring a different type. We were thus able to compare the following procedures: (1) intracapsular cataract extraction and iris clip implant (Federov type); (2) intracapsular cataract extraction and anterior chamber implant (Choyce type); (3) extracapsular cataract extraction and posterior chamber implant (Sinsky type).

Although each of the three consultants favoured one type of implant, they each used both of the other types at some time, so that the results do not reflect on individual surgeons.

Patients and methods

All patients who received an implant from May 1979 onwards to June 1983 and for whom there was a follow-up of at least six months were recalled to assess the success of the implant surgery they had undergone. The results were compared with a series of routine intracapsular cataract extractions performed during the same period of time.

During the four-year period from May 1979 to June 1983, 225 patients received an implant following cataract extraction. Of these, 181 were assessed. Sixteen patients had died and 28 were too ill or unable to attend. They received implants in the

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proportion shown in Table 1. Out of 181 patients seen with implants 100 were female and 81 male. The average age was 74.5 years and the average follow-up 17 months.

One hundred and eighty-one patients who had undergone routine intracapsular cataract extraction without an implant were selected by taking the consecutive case from the operating book. Of these 181, 110 were female and 71 were male. Their average age was 72.7 years and the average follow up was 18 months. Thus the two groups represent a similar cross section of our cataract patients.

Results

The visual acuity results show that 166 (92%) of all implanted eyes saw 6/12 or better when the vision was corrected as compared with 150 (83%) of all non-implanted eyes, which saw 6/12 or better with their aphakic correction. Fig 1 shows the visual results obtained with the three types of implant. There was no significant difference ($p=0.05$) between the three types of implant in either unaided or aided visual acuity.

Only 14 (8%) of the implanted eyes showed a visual acuity of less than 6/12. However, 31 (17%) eyes with no implant were unable to gain better vision than 6/12. In most cases, this was due to existing eye disease at the time of operation (Table 2) and does

Table 1 *Implant numbers*

Type of implant	Number	% of total
Iris clip	81	45%
Anterior chamber	44	24%
Posterior chamber	56	31%
Total	181	

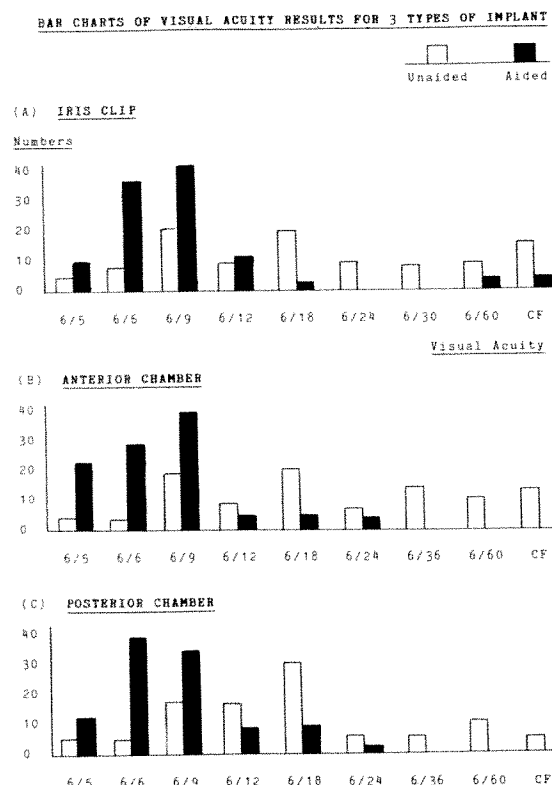


Fig. 1 Visual acuity results for three types of implant. CF=counting fingers.

not reflect on the method of surgery or the correction of aphakia. (Two cases of cystoid macular oedema were noted in the implanted eyes and these are discussed in the next section.)

Complications arose in 23 (13%) of the implanted eyes (three eyes had more than one complication) and in seven (4%) of the eyes following routine intracapsular cataract extraction. The analysis of complications was divided up into those occurring early either during the operation or in the immediate postoperative period (Table 3) and those occurring

Table 2 Causes of reduced visual acuity (<6/12)

	Implanted eyes	Non-implanted eyes
Senile macular degeneration	7	12
Cystoid macular oedema	2	—
Amblyopia	—	5
Chronic simple glaucoma	—	5
Diabetic retinopathy	—	2
Corneal decompensation	—	2
Central retinal vein occlusion	1	1
Retinal detachment	—	1
Others	4	3
Total	14	31

Table 3 Operative and postoperative complications

Procedure	Vitreous loss	Pupil block	Iris prolapse	Hypopyon	Raised intraocular pressure
Routine	3	—	—	—	—
Iris clip	2	1	1	1*	1†
Anterior chamber	1	—	—	2	2
Posterior chamber	—	—	1	1	—

*Plus vitreous loss.

†Also required repositioning.

Table 4 Late complications

Procedure	Capsule or membrane thickening	Corneal decompensation	Retinal detachment	Cystoid macular oedema	Re-positioning
Routine	—	2	2	—	—
Iris clip	2	—	—	1	7
Anterior chamber	—	—	—	1*	—
Posterior chamber	2	—	—	—	—

*Plus vitreous loss.

Table 5 Numbers of complications

Operation	Number	Percentage
Routine cataract extraction	7	4
Iris clip	16*	20
Anterior chamber	6*	14
Posterior chamber	4	7

*Three eyes suffered more than one complication.

later during the follow-up period (Table 4). Two other patients with anterior chamber lenses commented on some tenderness on touching the eye, but on the whole the patients were very satisfied with their operation.

The number of eyes in which complications arose is shown in Table 5. χ^2 tests were applied to these numbers with the following results. There was a significantly greater number of complications in eyes receiving an iris clip or an anterior chamber implant in comparison with routine cataract extraction. However, the posterior chamber implant procedure produced no significant increase in complications ($p=0.05$). In addition the posterior chamber implant procedure produced significantly fewer complications in comparison with the iris clip implant procedure but not in comparison with the anterior chamber implant procedure ($p=0.05$).

COST

With so much attention on expenditure in the

National Health Service (NHS) it was thought of interest to estimate the additional cost of correcting the vision of an aphakic eye by using an intraocular implant rather than by aphakic glasses. Two factors were considered relevant.

(1) *Operative.* There is no doubt that there is an increased use of both Healonid (containing sodium hyaluronate 10 mg/ml) to facilitate lens implantation and Miochol (acetylcholine 1% and mannitol 3%) to ensure good pupil closure when an implant is introduced as compared with routine cataract extraction. In this series Healonid was used in only 12 (7%) of the implant operations: five iris clip; six anterior chamber, and one posterior chamber. Miochol was used in 43 (24%) of the implant operations: 15 iris clip; 20 anterior chamber, and eight posterior chamber. These drugs are expensive: Healonid costs £30.00 a vial and Miochol £6.75 a vial, but their use is not routine.

(2) *Refractive.* The average cost to the NHS of an intraocular implant is £80.00. If a reading correction is required for the implanted eye, the spectacle lens will cost less than £6.00. The average cost to the NHS of a bifocal aphakic spectacle is £34.00. More often than not more than one lens is required and replacements are necessary.

Thus the average additional cost of correcting aphakia with an implant is shown to be less than £50.00.

Discussion

In 1978 iris fixation lenses were implanted most frequently.¹ At that time, Galin² reported that, though the visual acuities obtained with the iris clip implants were no different from those obtained by routine cataract surgery without implant, there was a significant increase in the incidence of dislocation and membrane formation. This is confirmed in our series. However, since 1980 the use of iris clip implants has declined in favour of the use of either anterior chamber or posterior chamber implants.

In some hands the anterior chamber implant gives excellent results. It has the advantage that it is best suited to an intracapsular cataract extraction, a technique which has been practised for years.³ Others have favoured an extracapsular technique combined with a posterior chamber implant. Several reports have been published comparing the advantages and disadvantages of intra- and extracapsular surgery,⁴

and, though there is evidence to suggest a lower incidence of cystoid macular oedema and of retinal detachment following extracapsular surgery, there is the incidence of thickening of the posterior capsule to be considered. The reported number of eyes requiring capsulotomy varies widely, from 5 to 50% after three years, and no long-term figures are yet available. In our series, with a short follow-up, only two patients showed a thickened capsule, that is, 4% after 18 months.

Data from the FDA report¹ show that posterior chamber lenses give significantly better visual acuity results than other types—but the report admits this may be the result of better case selection, as other implants would be used if operative complications arose during the procedure. In this hospital the extracapsular cataract technique combined with posterior chamber implant is now used as routine by all three surgeons cited in this report unless a specific contraindication exists.

CONCLUSION

In this paper it has been shown that the use of extracapsular cataract technique combined with the implantation of a posterior chamber lens is a safe procedure. The quality of vision thus gained is much better than with aphakic glasses. Useful vision returns immediately, and the patient is inconvenienced only by his few days in hospital. Though the procedure costs more than cataract extraction followed by aphakic glasses, the extra cost must be justified to meet patients' expectations, which are now very high indeed.

I am grateful to all the consultants at the Royal Victoria Hospital, Westbourne, for allowing me to study their patients and to Dr N Joshi, who helped to collect the data. I am also grateful to Mr M Robertson for statistical advice and to Mrs Jane Dunlop for typing the script.

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Hyaluronidase and sodium hyaluronate in cataract surgery

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SUMMARY The use of sodium hyaluronate in cataract surgery and intraocular lens implantation is often followed by a postoperative rise of intraocular pressure. A trial is described in which 10 patients underwent bilateral cataract extraction and Binkhorst intraocular lens implantation with the use of sodium hyaluronate. The enzyme hyaluronidase was instilled into the anterior chamber of the right eye only, to aid removal of sodium hyaluronate, and resulted in a statistically significant lowering of postoperative intraocular pressure in right eyes compared with left. Other uses of the enzyme are discussed.

Sodium hyaluronate (SH) is a viscoelastic material which has found use in many anterior segment and some posterior segment surgical procedures. It has been widely investigated and reported on.¹⁻³ When it has been used as an aid to intraocular lens (IOL) implantation, a sharp rise in intraocular pressure (IOP) in the first three postoperative days has been noted^{1,4} over and above that originally reported by Rich and colleagues following cataract surgery before the advent of SH.^{1,2}

Various techniques have been advocated to reduce this additional postoperative hypertension, including: (1) postoperative acetazolamide²; (2) postoperative timolol drops²; (3) intravenous mannitol, postoperatively and at the time of surgery³; (4) anterior chamber irrigation with balanced salt solution^{1,5}; (5) aspiration of SH with a wide-bore needle or Cavitron suction.^{1,4}

There are disadvantages and potential problems with all five of these methods. The postoperative remedies are often ineffective and/or slow to take effect,¹ and at times toxic to the patient.¹ Berson *et al.*⁶ demonstrated a substantial decrease in measured aqueous outflow facility following instillation of SH into the anterior chamber of enucleated human eyes. Acetazolamide, timolol, and intravenous mannitol are aimed at reducing the hypertensive effect of SH in the anterior chamber only after this outflow obstruction has occurred.

After IOL implantation SH can be irrigated out of the anterior chamber with balanced salt solution or

aspirated with a wide-bore needle or by Cavitron suction.^{1,1} In the study by Berson *et al.*⁶ irrigation of the anterior chamber with saline solution had only limited success in alleviating obstruction to outflow, and, while these methods may have clinical applications, their use following implantation of an anterior chamber iris clip lens may be hazardous. Sudden expulsion or aspiration, from a partly open section, of a large volume of SH could result in loss of anterior chamber depth and lens-endothelial contact or even vitreous loss. Yet SH offers such significant advantages in anterior/posterior segment surgery that any endeavours to reduce its unwanted postoperative side effects while retaining its surgical advantages would be welcome.

Hyaluronidase is an enzyme which cleaves SH into smaller fragments, and has been used experimentally in cadaver human eyes⁶ to degrade SH enzymatically, with dramatic results in reducing the hypertension following SH instillation. A reduction in trabecular meshwork obstruction and an increase in aqueous outflow facility was shown. Linn and Ozment reported some 35 years ago⁷ that the use of hyaluronidase was followed by a marked intraocular inflammatory reaction and suggested a potential risk to the corneal stroma. This was the result of the use of an enzyme containing impurities, but a highly purified enzyme is now available.

Our pilot studies showed that the instillation of hyaluronidase during intracapsular cataract extraction and IOL implantation, after the introduction of SH, reduced the expected postoperative hypertension and allowed the egress of SH from the

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anterior chamber in a controlled manner. The use of the enzyme in cataract surgery has been mentioned previously,³ but without the results of a clinical trial.

We describe a trial of the use of hyaluronidase to remove SH from the anterior chamber after intracapsular cataract extraction and Binkhorst IOL implantation.

Materials and methods

Ten consecutive patients underwent uncomplicated bilateral intracapsular cataract extraction with insertion of Binkhorst (Cilco) iris clip IOLs. In all cases the operation was bilateral under the one general anaesthetic. The average age of the patients was 76 years, range 56 to 85 years.

All cases had preoperative endothelial cell counts by specular microscope photography with the Heyer-Schulte microscope system. The surgery was carried out by the two authors under general anaesthesia. One surgeon performed both operations on a particular patient using an identical procedure for each eye. The choice of which eye was operated on first depended on which side the assistant's microscope was found to be at the start of surgery. This ensured a random selection beyond the surgeon's control. An ab externo approach, under a limbal-based conjunctival flap, was employed. Two peripheral iridectomies were performed, followed by instillation of α -chymotrypsin and a cryoextraction of the lens. SH was then used to form the anterior chamber, and to coat the IOL, which was secured, after placement, with a 10/0 nylon iris suture. Miochol (acetylcholine 1%, mannitol 3%) was instilled. The wound was closed with at least nine 8/0 virgin silk sutures; 0.5 ml of hyaluronidase made up by dissolving 1500 units in 1 ml of sterile water was then instilled at intervals into the anterior chamber, through the secured wound, of the right eyes only. One drop of topical 4% pilocarpine and a subconjunctival injection of methylprednisolone (Depomedrone) completed the procedure.

Postoperatively the IOP was measured daily from the first day until discharge, usually on the sixth postoperative day, and on each outpatient visit, by members of staff other than the authors. Postoperative medication consisted of a topical steroid-antibiotic combination four times per day. If the IOP was above 30 mmHg in either eye, systemic acetazolamide was added, and withdrawn as the pressure

came down. Endothelial cell counts were repeated on average four months postoperatively, with a range from 2½ to 6 months.

Results

The results are summarised in Tables 1, 2. Statistical analysis by the Wilcoxon matched-pairs signed-ranks test indicated a significant difference between IOP levels in the right and left eyes on days 1 and 2, but the significance was reduced on day 3. Preoperatively and by day 6 there was no significant difference.

Discussion

The postoperative rise in IOP which may occur after cataract surgery has been extensively studied by Rich and colleagues^{6,7} among others. Many workers have reported on the postoperative ocular hypertension following the use of SH.¹⁻⁴ It was in an attempt to reduce this pressure rise that the enzyme hyaluronidase was used to aid in the safe removal of SH from the anterior chamber.

Apart from case 1, in which the right eye showed a marked pigment dispersion in the anterior chamber, all cases showed a much lower postoperative IOP in the right eye than in the left on days 1 to 3. By the sixth postoperative day this pressure difference had largely disappeared.

The intraocular levels postoperatively in the left eyes were higher than reported in some series, for example Percival,¹⁰ but this is a function of the comparatively large number of sutures used in an attempt to achieve watertight closure and to avoid wound rupture, which featured in the previously reported cases.¹⁰ Our postoperative intraocular pressure levels in the left eyes were similar to those found by Rich *et al.*⁷

The intraocular levels in the right eye were lower than that recorded by Rich *et al.*⁷ despite a similar

Table 1 Average percentage endothelial loss

Right eye	10.25
Left eye	8.25

By the same statistical analysis there was no significant difference.

Table 2 Pre- and postoperative intraocular pressure levels

	Mean of intraocular pressures in mmHg (standard deviations in brackets)		Level of significance
	Right	Left	
Preoperative	14.5 (2.3)	14.2 (2.3)	
Postoperative			
Day 1	21.3 (6.0)	36.1 (9.3)	p<0.02
Day 2	15.3 (5.2)	23.7 (6.6)	p<0.01
Day 3	15.5 (8.5)	20.6 (7.6)	0.1>p>0.05
Day 6	14.3 (5.9)	14.3 (3.2)	
2-4 weeks	14.6 (2.7)	15.3 (1.7)	
2-3 months	14.1 (3.0)	15.0 (3.6)	

technique, and this may be the result of a dual effect of hyaluronidase. As well as aiding in the removal of SH from the anterior chamber the enzyme may also have a direct effect on the trabecular meshwork, increasing outflow facility. Many workers, including Peterson and Jocson¹¹ and Knepper *et al.*¹² have reported on the decreased outflow resistance which follows perfusion of the anterior chamber with hyaluronidase.

The final visual outcome was comparable in both groups, with the right eye achieving a marginally better standard. Apart from patient 10, who was known preoperatively to have bilateral disciform macular degeneration, the average visual outcome was 6/12, with a range from 6/6 to 5/60. Two patients developed cystoid macular oedema; in both cases the left eye was more severely affected.

Postoperative endothelial cell counts indicated a comparable cell loss in the right and left eyes, and the percentage loss was in line with previously published results¹³ with the same instrument.

We thus suggest that instillation of hyaluronidase is a quick, easy, and safe method of reducing the postoperative ocular hypertension following cataract surgery involving SH and IOL implantation. The enzyme may well have other indications, for example, following anterior segment trauma, penetrating keratoplasty, or glaucoma surgery. In these situations SH is of value in maintaining tissue separation, but its presence can make it difficult to decide whether a wound is watertight or merely SH-tight. This problem has been commented on by Roper-Hall.¹⁴

To use an agent that is known to cause a postoperative rise in IOP during glaucoma surgery is a questionable decision in spite of its manipulative advantages during surgery. If, however, the postoperative rise in IOP can be abated, many of the potential objections to its use are removed. Both trabeculectomy and goniotomy are particular examples, the first to restore the patency of the anterior

chamber after decompression of the eye, the second to maintain a deep anterior chamber for the safe performance of the operation, in the knowledge that the SH can be completely removed and replaced by air to demonstrate its removal.

We are most grateful to Dr N Price for the specular microscopy; the Department of Hospital Statistics, Queen Elizabeth Hospital, Birmingham, for their advice on and help with the statistical analysis, and to Mrs C Rawlins for her secretarial help.

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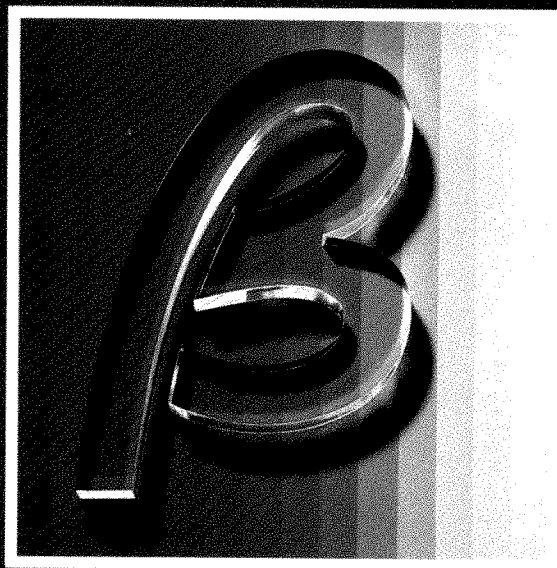
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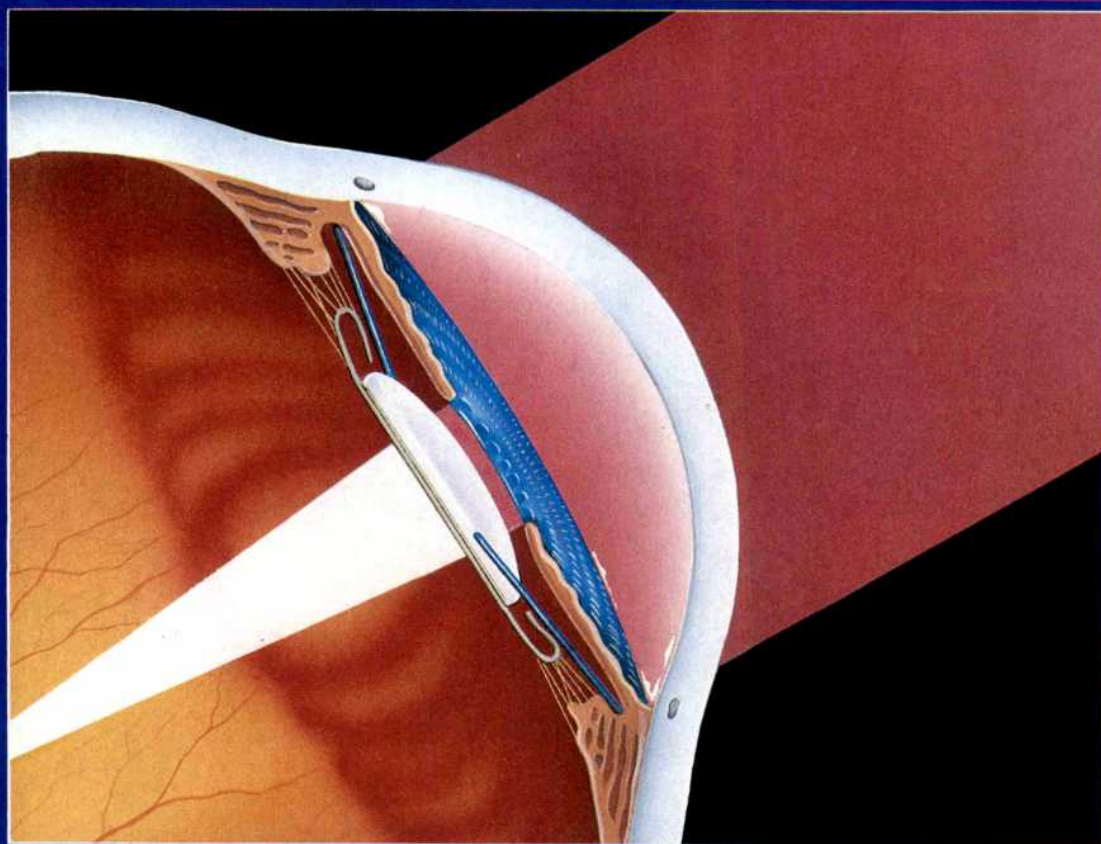
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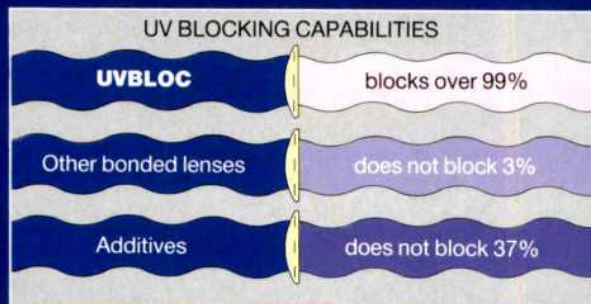
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Rise in lens temperature on exposure to sunlight or high ambient temperature

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SUMMARY The effect of increase ambient temperature and sunlight on the temperatures of the rabbit lens and posterior chamber (PC) aqueous humour was measured by needle thermistor probes while the rectal temperature was monitored. Exposure of rabbits to sunlight (35°–42°C), in New Haven, Connecticut, USA, resulted in significant temperature increases in PC (4.3°C), lens (3.2°C), and rectum (2.3°C). Returning animals to the shade resulted in a progressive decrease in the temperatures of the PC or lens in the tested eye, but repeating exposure to sunlight resulted in significant increases of the baseline (PC) temperature (increase 2.68°C) of the second eye. Exposure of rabbits to sunlight at 49°C in Chandigarh, India, resulted in increased PC temperature of 4.48°C after 9 minutes. Increased PC and lens temperatures after exposure to sunlight are due both to an ambient temperature effect through the cornea and to increased body temperature. In dry and hot tropical areas of the world temperature increases in the lens after exposure to sunlight may initiate or accelerate the formation of senile cataracts.

The possible association of senile cataracts with incident radiant energy of any wavelength on the lens was first proposed by Duke-Elder in 1926.¹ Goldmann in 1933 induced posterior subcapsular cataracts in animals by prolonged exposure to heat.² More recently several studies have revealed that lens protein or tryptophan solution exposed to sunlight or ultraviolet light will change its colour and fluorescence in a similar way to that of cataractous lenses.^{3,4} Furthermore, photoperoxidation of kynurenine, a tryptophan derivative, may act as a photosensitizer, mediating light induced non-disulphide cross-linking of protein as found in human cataracts.⁵ Ultraviolet light has been implicated in the possible sunlight effects, either as initiator or accelerator of cataracts in sunny or tropical areas of the world.^{6,7} From a recent analysis of the epidemiological data from Hawaii⁸ it appears that other physical factors besides ultraviolet are involved in cataractogenesis. In this regard Minassian *et al.*⁹ found that dehydration crisis from heat stroke increases the risk of cataracts by a factor of 1.75 and that exposure to both heat stroke and severe diarrhoea increases by 15-fold the

risk of having cataract. It appears that high ambient temperature may play a part in cataract formation.

The lens is seriously influenced by increased ambient temperature. Voaden¹¹ found that lysis and cell death occurred in cultured rabbit lens epithelial cells exposed to 38°C or higher. Edwards *et al.*¹² found cell death in the central nervous system and cataract formation in guinea-pig embryos following maternal exposure for 15 hours to 42–42.5°C on the twenty-first day of gestation.

The presence of a temperature gradient between corneal surface and vitreous cavity, which disappeared if the lids were kept closed, was shown in rabbits by Schwartz,¹³ who also noticed that lowering environmental temperature decreased lens temperature.¹⁴

The thermal energy generated by sunlight might have a major role in cataract formation, as the lens is placed behind the iris pigment epithelium. Increases in temperature in the posterior chamber during experimental xenon arc or laser photocoagulation resulted in cataract formation.¹⁵ To determine the role of sunlight on the temperatures of the lens and posterior chamber aqueous humour rabbits were exposed to mid-day sunlight. However, concomit-

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ant body temperature increases were found in the animals due to environmental heating. This led to a series of experiments conducted indoors which helped to clarify the role of environmental heating on lens and posterior chamber temperatures.

Material and methods

Pigmented rabbits weighing about 2.5 kg were anaesthetised with intravenous pentobarbitone (Nembutal) in doses of 20 mg/kg body weight. A lid retractor was placed in one eye. The posterior chamber was entered through the sclera approximately 2 mm from the corneoscleral limbus with a 24 gauge thermistor needle probe (No. 524) with time constant of 0.1 second plugged to a model 46 TUC telethermometer (YSI Co.).¹⁷ About 7 mm of the metallic probe was inserted into the eye; the remaining part was covered with a plastic tube to minimise the heat loss or gain causing the error reported by Fatt and Forester.¹⁸ A similar probe was inserted into the anterior lens cortex through the opposite side of the same eye. The body temperature was recorded by a rectal probe (401) with a time constant of 7 seconds. Air temperature was measured with a mercury-in-glass thermometer certified to 0.1°C which had been used to calibrate the probes.

OUTDOOR EXPERIMENTS

(a) In New Haven, Connecticut. The experiments were conducted on six pigmented rabbits (12 eyes)

during the month of July on the roof of a 10-story building with walls shielding the area from wind and totally exposed to sunlight between 11.30 am and 12.30 pm. Ambient temperatures in the shade varied from 28 to 30°C and in the sunlight from 35 to 42°C during the course of the experiments. In each experiment temperatures were recorded from eye No. 1 with one probe in the lens, another one in the posterior chamber, and the third in the rectum for at least 9 minutes. Then the animals with the probes in place were moved to the shade, and the recording continued for at least 7 minutes. After the conclusion of the experiments on eye No. 1 we repeated the same procedure on eye No. 2.

(b) In Chandigarh, India. The experiments were conducted on six pigmented rabbits in a large courtyard between 11.30 am and 12.30 pm. Ambient temperatures of 37°C in the shade and 49°C in the sunlight precluded experiments lasting longer than 20 minutes owing to intense dehydration of the investigators and probably of the experimental animals.

(c) Also in India under similar circumstances another experiment was conducted on the eyes of one monkey. With the same probes the posterior chamber and lens temperatures were recorded. The effect of a 1% transmission filter was tested.

INCUBATOR EXPERIMENTS

The rabbit was placed inside an infant incubator (Air Shield Co.) and the temperature probes were placed in the posterior chamber, the lens, and the rectum. A

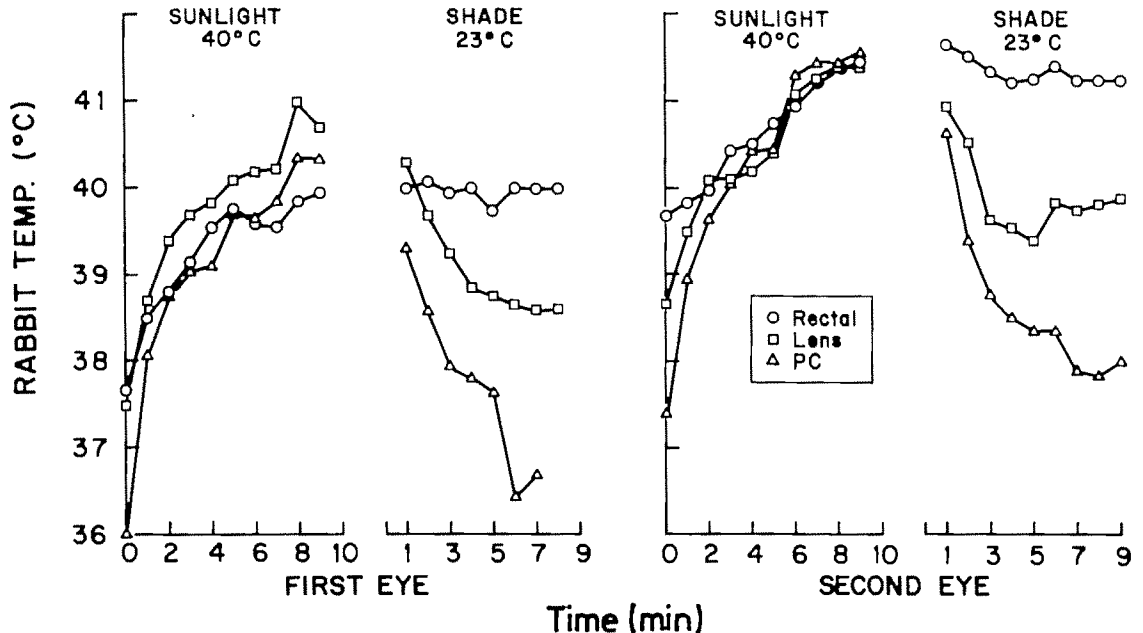


Fig. 1a Representative diagrams of the experiments in pigmented rabbits conducted in (a) New Haven (see Fig. 1b).

mercury-in-glass thermometer was used to measure incubator temperature. The incubator temperature was raised to 50°C by exposure to a heated air blower attached to one of the incubator's portholes. Temperatures were recorded every minute for at least 9 minutes. When heating was discontinued, the incubator doors were opened to allow equilibration with the room temperature. The recording of temperature was continued every minute during the following 7 minutes. The probes were transferred to the second eye and the same procedures were repeated as above. The experiments were done with the animal in the incubator on one occasion and with only the head inside or outside the incubator on other occasions.

Results

In the outdoor experiments performed in New Haven, where the mean ambient temperature in the shade was 29°C and in the sun 38.5°C, exposure of the animal to sunlight resulted in a progressive increase of the temperatures of the posterior chamber, the lens, and the rectum. The rise in these temperatures recorded from eye No. 1 was as follows: (a) in the posterior chamber 4.3°C, (b) in the lens 3.2°C, (c) in the rectum 2.3°C (Fig. 1, Table 1). Exposure of the animals to stronger sunlight in a warm environment such as our experiment in India, where the temperature was 49°C, resulted in slightly higher temperatures in the posterior chamber (4.48°C) and the lens (3.5°C) (Fig. 1, Table 1). The temperature recordings from the posterior chamber of the two eyes of a monkey rose from 36°C to 41.5°C after approximately 9 minutes of exposure, and when a 1% Kodak filter was introduced the posterior chamber temperatures dropped to 40°C (Fig. 2).

When we did the experiment with the whole body inside the incubator, when the incubator temper-

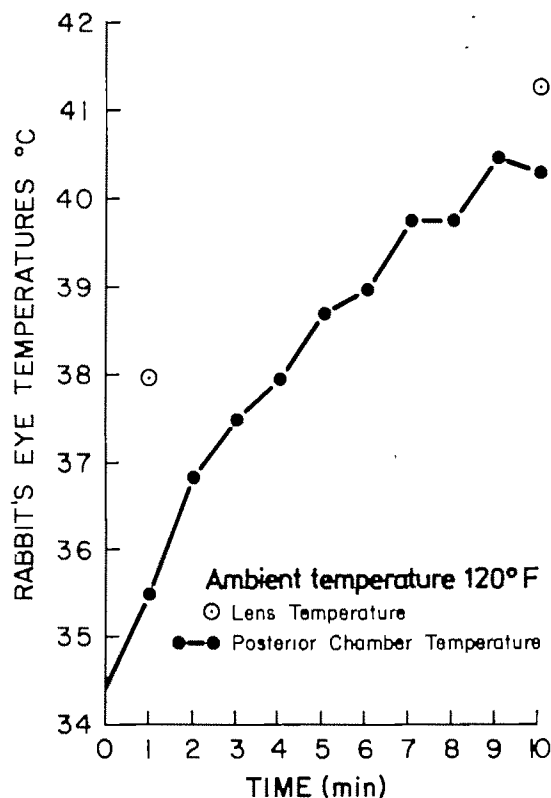


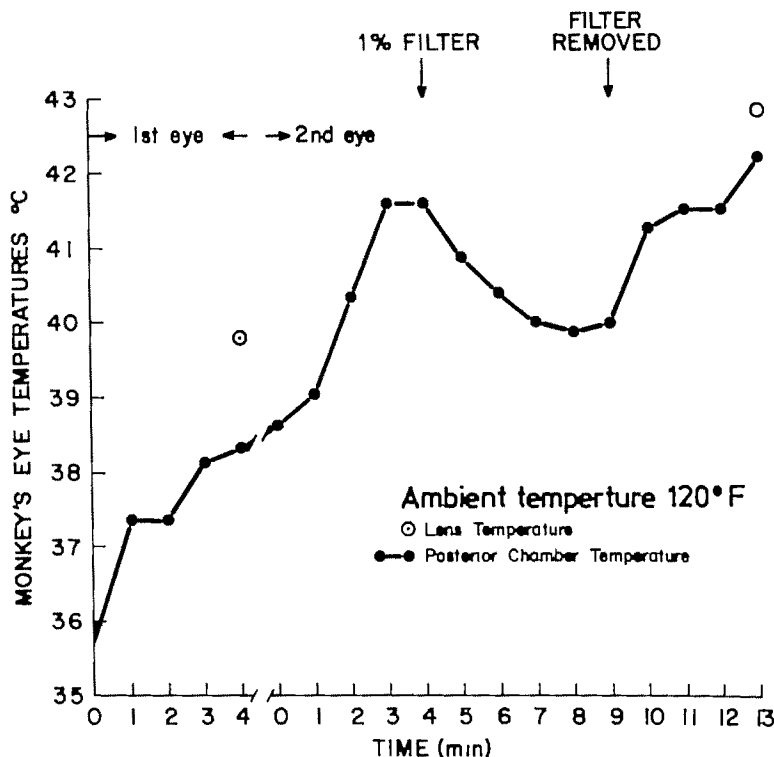
Fig. 1b and India On the abscissa is shown the exposure time to sunlight or to shade in minutes and on the ordinate the corresponding changes in rectal, lens, and posterior chamber temperatures.

ature was higher than that of the field experiment, we obtained less rise in the temperatures of the posterior chamber, the lens, and the rectum. This points to the significance of direct exposure to sunlight in raising the eye and body temperatures. The rise in these

Table 1 Posterior chamber, lens, and rectal temperatures ($\pm$ SD) recorded from eye No. 1 and eye No. 2 of pigmented rabbits, comparing the effect of direct exposure to sunlight with exposure to a heated environment

No. of animals			Duration in minutes				Temperature recorded in °C				
			Posterior chamber		Lens		Rectal		Ambient		
Eye 1											
Baseline temperature		6	—		36.02±0.59		37.50±0.45		37.65±0.42		29±0.5
Sunlight experiment											
New Haven, USA		6	9		40.32±0.67		40.7±0.54		39.97±0.45		38.5±0.4
Chandigarh, India		6	9		40.50		41.00				49±1.1
Indoor experiment		6	9		38±0.37		38.38±0.41		39.42±0.25		49.17±0.80
Eye 2											
Baseline temperature		6	—		38.7±0.47		39.7±0.18		41±0.36		45.75±1.56
Sunlight experiment											
New Haven		6	9		41.55±0.54		41.47±0.42		41.45±0.38		50±0.0
Indoor experiment		6	9		38.85±0.35		39.73±0.21		40.50±0.24		38.5±0.4

Fig. 2 Representative diagram of the experiments conducted on a monkey in India. On the abscissa is shown the exposure time to sunlight in minutes and on the ordinate the corresponding changes in posterior chamber and lens temperatures. Note the significant reduction of posterior lens temperature after covering the eye with a 1% transmission filter during exposure to sunlight.



temperatures recorded for eye No. 1 was as follows: (a) in the posterior chamber 2.32°C (b) in the lens 2.32°C , and (c) in the rectum 0.55°C (Table 1). When the temperature was allowed to drop (in both outdoor and indoor experiments) for 7–8 minutes, the recorded temperatures decreased to a degree higher than the baseline temperature at zero time in eye No. 1. The outdoor experiments (Table 2) tended to give the higher recordings.

The final recordings at the end of 9 minutes from eye No. 2 (Table 1) showed higher temperatures in the posterior chamber, lens, and rectum than were

obtained at the end of 9 minutes in eye 1 in both outdoor and indoor experiments. These were attributed to the retained temperature from the experiment done in eye No. 1. Thus prolonged exposure to sunlight or a heated environment will increase eye and body temperatures.

In order to dissociate the effect of body temperature from the environmental temperature an experiment was performed by placing the head of the rabbits either inside or outside the incubator. Comparing the recordings from the head-out experiments in both eye No. 1 (minimal rise) and eye No. 2

Table 2 Posterior chamber, lens, and rectal temperatures ($\pm\text{SD}$) recorded from eye No. 1 and eye No. 2 of pigmented rabbits at the end of 7–8 minutes after discontinuing sunlight or heat

	No of animals	Duration in minutes	Temperature recorded in $^{\circ}\text{C}$			
			Posterior chamber	Lens	Rectal	Ambient
Eye 1						
Baseline temperature	6	—	36.02 ± 0.59	37.5 ± 0.45	37.66 ± 0.42	29 ± 0.5
Sunlight experiment						
New Haven, USA	6	8	36.70 ± 0.37	38.6 ± 0.1	40.00 ± 0.51	29 ± 0.5
Indoor experiment	6	8	37.53 ± 0.33	38.17 ± 0.24	39.83 ± 0.25	33.33 ± 1.22
Eye 2						
Sunlight experiment	6	7	37.9 ± 0.50	39.76 ± 0.11	41.23 ± 0.17	29 ± 0.5
Indoor experiment	6	7	37.45 ± 0.82	38.65 ± 0.48	41 ± 0.43	31.5 ± 2.86

Table 3 Recordings from posterior chamber, lens, and rectum from eye No. 1 and eye No. 2 of pigmented rabbits after 9 minutes exposure either totally or partially to a heated incubator.

	Temperature recorded in °C				
	Posterior chamber	Lens	Rectal	Incubator	Room
<i>Eye 1</i>					
Baseline temperature	36.02	37.5	37.65		29±0.5
Total body inside	38	38.38	39.42	49.17	
Only head inside	37	37.5	37.8	50	25-27
Only head outside	33	35.5	39	50	
<i>Eye 2</i>					
Total body inside	38.85	39.75	40.50	48.75	
Only head inside	37.8	38.5	39	50	25-27
Only head outside	37.5	38.5	39	50	

(significant rise) with those from total-body and head-in experiments clearly illustrates the role of rise in both body and ambient temperatures on the temperatures of the lens and the posterior chamber (Table 3).

Discussion

Evidence indicating a possible role of sunlight and ultraviolet light on the formation of senile cataract had been summarised by Zigman.⁶ The visible and infrared components of sunlight can raise posterior chamber and lens temperatures, as shown in experiments on heat absorption by the iris and their effect on the lens.¹⁰ Our experiments represent the first measurement of lens and posterior chamber temperatures under experimental conditions which may simulate those of human eyes exposed to sunlight.

The rise in posterior chamber and lens temperatures of pigmented rabbits exposed to sunlight was due to a variety of factors, some of which were analysed in the experiments. The outdoor experiments in New Haven revealed that 9 minutes' exposure to sunlight resulted in an increase in lens temperature which was maintained even after exposure to sunlight had been discontinued. Furthermore, it would appear that, in rabbits which were already exposed to sunlight and had an increased body temperature, the temperature in the second eye rose to levels above 41°C, which could accelerate a variety of metabolic reactions. If heat is accumulated, the higher temperatures could accelerate or initiate chemical cataractogenic processes such as glycosylation or carbamylation of lens proteins.

The rise in lens and posterior chamber temperatures following exposure to sunlight represented the combined effect of thermal absorption by the pigment epithelium of the iris plus the temperature increases which resulted from exposure of the eye and the body to a warmer environment. The in-

creased body temperatures which resulted from exposure to sunlight were analysed by the indoor experiments in the incubator. It appeared that a 1.77°C increase in body (rectal) temperature is associated with increased posterior chamber and lens temperatures by 1.98°C and 0.88°C respectively. This rise in lens temperature resulted from both transmitted body heat and environmental heat. However, in rabbits exposed to sunlight (New Haven), higher rises in posterior chamber (4.3°C) and lens (3.2°C) temperatures were found despite an increased in body (rectal) temperature of 2.3°C. Thus, the combined body and environmental factors did not account for the whole rise but for approximately 30% of the sunlight-induced rise of lens temperature. This was substantiated by the results from exposure to high environmental temperatures with the head inside or outside a heated incubator.

Temperature increase induced modification in the distribution of lens crystallin. Lu-Ku-Li demonstrated that the lens protein subfractions were altered by increasing the temperature during gel filtration chromatography from 8°C to 40°C.⁹ He found a gradual disappearance of the B₆ crystallin and to a less extent of γ crystallin with rise in temperature and reappearance of a new high molecular weight β crystallin which was not present in the profile obtained at 8°C. The SH moiety of cysteine was found to be essential for the formation of this high molecular weight protein. Voaden found lysis and death of the rabbit lens epithelial cells in cell culture when exposed to 38°C or higher.¹¹ In our experiments we found that raising the incubator temperature to 50°C for a short period of time produced a 0.88°C rise in lens temperature, while exposure to sunlight at 40°C led to a 3.2°C rise in lens temperature. The prolonged temperature rise which occurs in very warm countries may be sufficient to change the metabolism and the transparency of the lens. However, the contribution of long-term high-temperature

exposure to cataract formation is not known. High lens temperatures do accelerate lens metabolism and may effect lens elasticity. Miranda found that presbyopia is directly correlated with ambient temperature rather than exposure to ultraviolet light.²⁰ Moreover in a study conducted in the Punjab the incidence of cataract was found to be greater in the plains than in the mountains, where the ultraviolet light is higher and the temperature is lower.²¹ We believe that the development of human senile cataract is better correlated with both high ambient temperature and exposure to sunlight (ultraviolet and infrared). The recent studies of Minassian *et al.*¹⁰ associated the increased ambient temperature in various areas of the Punjab with the risk of cataracts due to diarrhoea, heat stroke, or both. Increased carbamylation of lens protein has been associated with severe diarrhoea.²² Our studies provide experimental evidence for the role of ambient temperature on the lens and on the possible acceleration of the cataract forming process(es) by high temperature.

In summary, our results give evidence that both body and ambient temperature increase the temperature of the lens and that exposure to sunlight results in an additional temperature increase.

The authors thank the Department of Ophthalmology at the Post-graduate Institute of Medical Education and Research in Chandigarh, India, for their help and Professor M Pandolfi, King Faisal University, Dammam, Saudi Arabia, for his comments

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Congenital corneal staphyloma: clinical, radiological, and pathological correlation

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SUMMARY A 2-year-old child was referred because of a prominent blind left eye with an opaque cornea. Although extraocular extension of a retinoblastoma was an initial diagnostic possibility, computed tomography (CT) showed only a large globe with a corneal staphyloma. Because of the cosmetically unacceptable appearance the involved eye was enucleated. The clinical, CT, and histopathological features of congenital corneal staphyloma are discussed, as well as the possible pathogenic mechanisms.

Congenital corneal staphyloma is a rare condition. It is presumed to be a developmental abnormality, characterised by an opacified, ectatic cornea that protrudes forward between the eyelids.^{1,2} The anterior segment of the involved eye is usually markedly abnormal. The condition can be either unilateral or bilateral. We report here the case of a child with a severe unilateral form of corneal staphyloma and review the clinical, radiological, and pathological features of this condition.

Case report

A 26-month-old Guatemalan girl was examined at the Oncology Service at Wills Eye Hospital in March 1984. She was a native Mayan Indian villager specifically brought to the United States for treatment of her eye condition. The past ocular and medical history was therefore incomplete. Apparently she was the product of a normal, full-term pregnancy except that the mother had an intestinal illness during the eighth month. The child was born at home with only a midwife present. At 5 days of age both eyes had a bloody, purulent discharge, which was successfully treated with topical antibiotics. At 2 months of age an opaque film was noted on the left cornea. She was seen for the first time by a physician at age 26 months. The child was sent to the United States and subsequently to the Oncology Service for treatment of possible advanced retinoblastoma.

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On examination the child had normal fixation and following movements of the right eye but no vision in the left. The right eye was completely normal. Examination of the left eye revealed a protruberant corneal cone bulging 10 mm forward from the normal limbal plane and extending anteriorly through the lid fissure. The corneal surface was yellow-white and appeared keratinised. The corneal diameter appeared much larger than normal. The conjunctiva was clear. No structures could be seen posterior to the cornea.

Ultrasonography revealed a large eye, 27 mm in anteroposterior length, with an abnormal anterior segment but apparently normal retina and vitreous.



Fig. 1 Orbital CT scan showing ectatic, protruding cornea and enlarged anterior segment. Lens and posterior segment appear normal and without calcification.

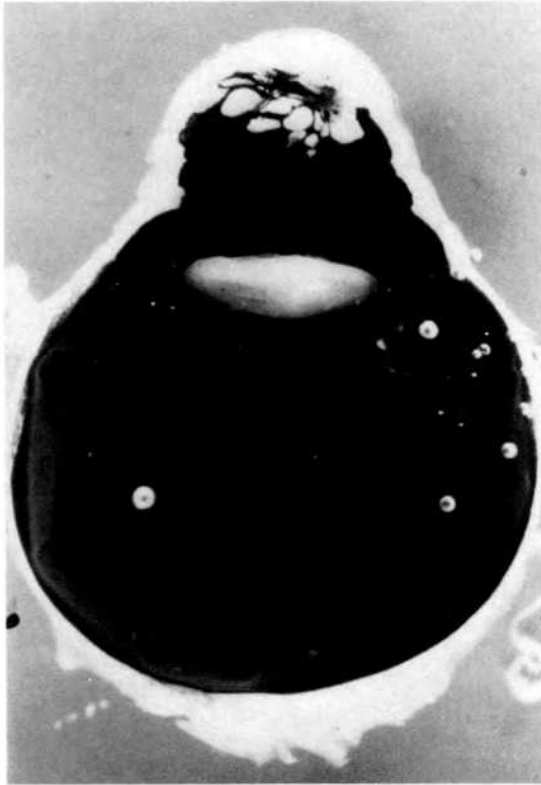


Fig. 2 Gross sectioned globe demonstrating iris tissue adherent to posterior cornea.

Computerised tomography (CT) showed an out-pouching of the globe's anterior aspect (Fig. 1). There was no contrast-enhancing abnormality or evidence of fatty tissue density in the anterior segment. There was no intraocular calcification. The right eye and both orbits were normal.

The diagnosis based on the above findings was congenital corneal staphyloma. Because of the lack of vision, the chances of pain from secondary glaucoma, and the cosmetic deformity in a unilateral presentation, it was elected to enucleate the left eye. After uneventful surgery and the fitting of a prosthesis the patient returned to Guatemala.

PATHOLOGY

The enucleated left globe measured 31×24×24 mm. The horizontal and vertical corneal dimensions were 16 and 14 mm respectively. The opaque-tan cornea projected forward as a cone for 12 mm (Fig. 2). The lens and posterior segment were normal, except that the optic nerve was severely cupped.

Microscopic examination of the left eye showed central corneal ectasia. The peripheral cornea was thickened with irregular epithelium due to rete pegs,



Fig. 3 Examination of the peripheral cornea. Note the rete pegs, vascularised stroma, and adherence of the atrophic iris resulting in total anterior synechiae. (Haematoxylin—eosin, ×15).

projections of the epithelium into the vascularised superficial stroma (Fig. 3). The central cornea showed keratinisation. Bowman's membrane was thin and atrophic, and there was a mild lymphocytic infiltration surrounding blood vessels which were in the stroma (Fig. 4). Descemet's membrane and the endothelium were completely absent (Fig. 5). The posterior aspect of the cornea was entirely lined with atrophic iris tissue which obliterated the anterior chamber (Fig. 6). The lens and vitreous were normal. The retina showed thinning of the ganglion cell and nerve fibre layers. There were a few lymphocytes round the retinal blood vessels. The optic nerve was severely cupped, with retrodisplacement of the lamina cribrosa. A mild proliferation of astrocytes was present in the substance of the nerve.

The final pathological diagnosis was congenital corneal staphyloma, corneal vascularisation and keratinisation, absence of Descemet's membrane, total anterior synechiae, angle-closure glaucoma, and cupping of the optic disc.

Discussion

Congenital corneal staphyloma typically presents in the young child as an opaque, ectatic corneal pro-

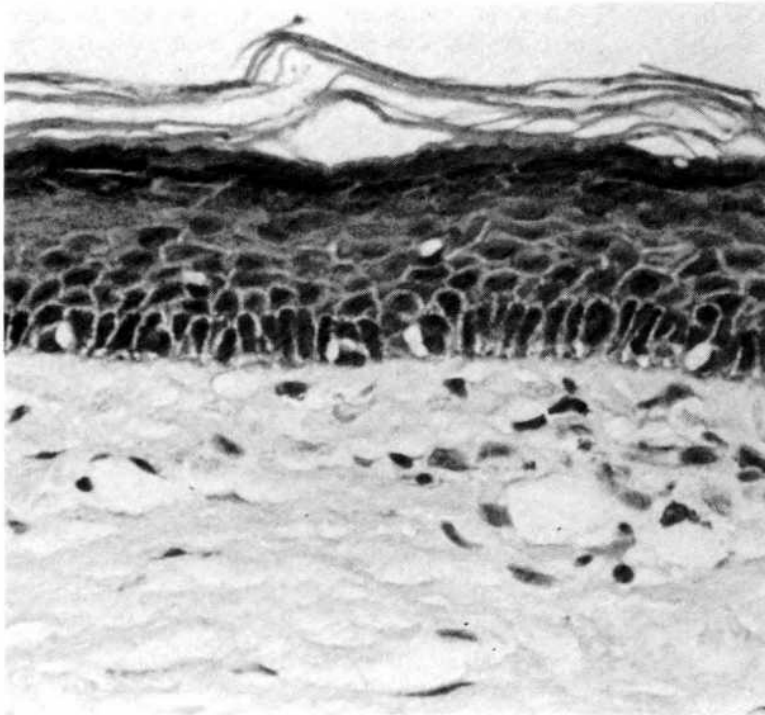


Fig. 4 The central anterior cornea shows keratinisation, abnormal epithelium, and lack of Bowman's membrane. (Haematoxylin—eosin, $\times 60$).

trusion lined on its inner surface by atrophic iris.^{1,14} Secondary angle closure resulting from total anterior synechiae leads to elevation of the intraocular pres-

sure and optic disc cupping. Protrusion of the bulging cornea between the eyelids can result in exposure keratitis, epithelial metaplasia, and keratinisation.

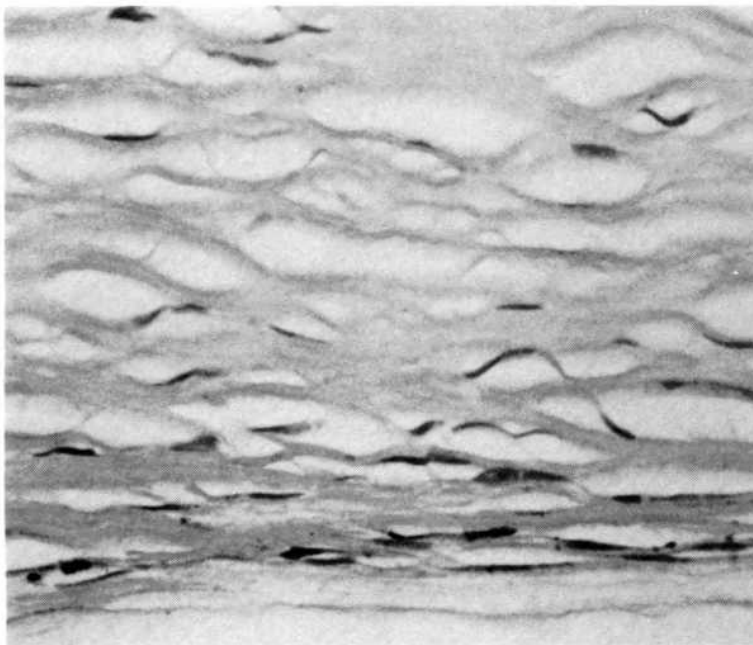


Fig. 5 Examination of the central posterior cornea through the pupil. Note the complete lack of Descemet's membrane and the endothelium. (Haematoxylin—eosin, $\times 60$).



Fig. 6 The angle shows total peripheral anterior synechiae obliterating the anterior chamber. The ciliary body is markedly atrophic. (Haematoxylin—eosin, $\times 5$).

Keloid formation has been reported to occur in staphylomatous cornea, presumably as a response to chronic corneal inflammation.⁵ Dermis-like choristomas arising from the ectatic corneas have also been reported.⁶

Histopathological and electron microscopic study of eyes with congenital corneal staphylomas characteristically shows absence of Descemet's membrane and corneal endothelium.² Inflammatory cells are notably absent in the stroma of the staphylomatous cornea in many cases. The absence of corneal endothelial cells combined with the lack of stromal inflammatory changes suggests that congenital corneal staphyloma is developmental rather than inflammatory in origin.² Congenital corneal staphyloma, like Peters' anomaly, is now presumed to be due to failure of the normal migration of neural crest cells. According to this view it is simply a more extreme form in the spectrum of central anterior segment mesenchymal dysgenesis than is Peters' anomaly.^{2,7} The combination of congenital corneal staphyloma with the median cleft face syndrome supports this view and puts the abnormal differentiation at the 17 to 20 mm stage of development (approximately seven weeks' gestation).⁸

Our patient fits both the clinical and histological definition of congenital corneal staphyloma. Nevertheless, in view of the child's vague postnatal history, the sequelae of a perforated corneal ulcer could also be considered as a possible explanation for this presentation. However, the total lack of endothelium

and Descemet's membrane, as well as the absence of a demonstrated perforation site, militates against this diagnosis.

In view of the severe cosmetic deformity of this blind, glaucomatous eye and the normal condition of the fellow eye we considered enucleation to be the most appropriate treatment. Although most eyes with congenital corneal staphyloma have come to enucleation, some success in treating the milder forms of this disorder with penetrating keratoplasty has recently been reported.² All bilateral cases of congenital corneal staphyloma probably warrant a surgical attempt to salvage some vision in at least one eye.

We believe this paper reports the first use of computerised tomography in the evaluation of corneal staphyloma. It was far more helpful than contact ultrasonography in showing the anterior segment abnormality and excluding other diagnoses such as dermoid cyst or retinoblastoma. It should be especially useful in differentiating the milder forms of corneal staphyloma from other associated disorders with buphthalmos and corneal opacification. Furthermore, if keratoplasty is being considered, the information provided may prove invaluable in the decision to proceed as well as in planning the surgery.

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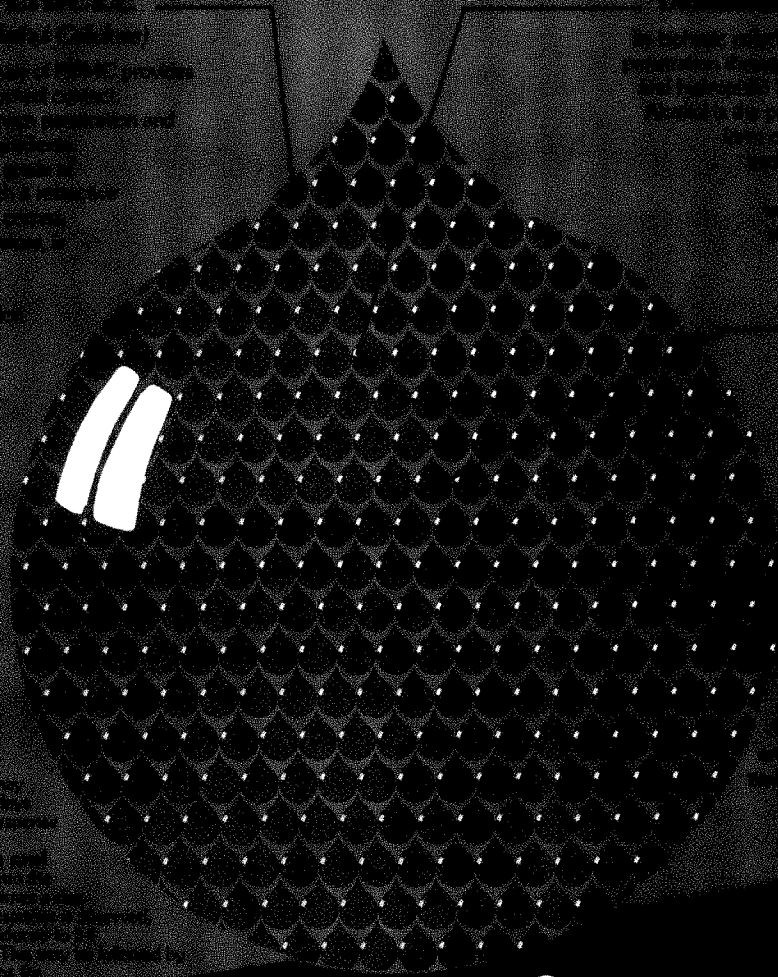
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Development of an immunofluorescence test for the serodiagnosis of herpes zoster ophthalmicus

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SUMMARY An indirect immunofluorescence test has been developed and evaluated for the serodiagnosis of herpes zoster ophthalmicus (HZO) by the detection of antivariella zoster virus (VZV) antibody. The results show that, in patients with HZO, anti-VZV IgG antibody titre usually rises rapidly after onset. One hundred and seven of the 134 sera (80%) from patients with a clinical diagnosis of HZO had an anti-VZV IgG titre of ≥ 256 , and IgM antibody at a level of 1 in 8 was present in six of them. In comparison only two of the 216 sera (1%) from patients with a clinical diagnosis of ocular infections other than those caused by VZV had such IgG titres. It was concluded that, on the basis of results of a single sample of serum, it is possible to make a provisional diagnosis of HZO with a high degree of confidence.

Varicella-zoster virus (VZV) can affect any part of the eye with varying degrees of severity, producing rather a pleomorphic clinical picture. The clinical diagnosis of HZO, when associated with typical skin lesions presents no problems. However, sometimes there are minimal or no skin lesions or there is an

atypical rash which may mimic that of herpes simplex virus (HSV).¹ Hence a rapid and sensitive laboratory diagnosis is important in the differential diagnosis of these atypical cases.

Several laboratory tests are available for the diagnosis of VZV infections. Demonstration of viral antigens in clinical specimens is rapid, but it is useful only during the first few days of infection when

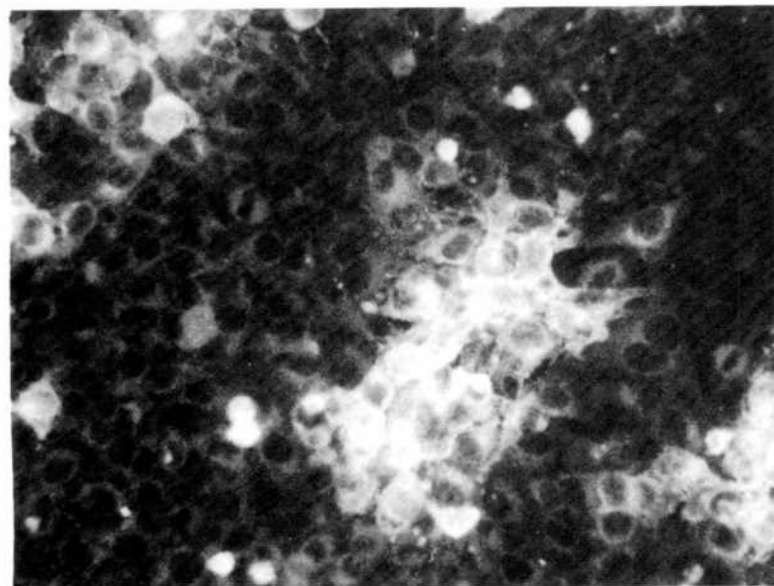


Fig. 1 Brightly fluorescing VZV infected cells growing as plaques in HeLa cell monolayer. ($\times 540$).

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vesicles are present.² Virus isolation in cell culture is a definitive means of diagnosis, but this is possible in only a few cell lines and only during the first few days of infection. Several serological tests are available, including immunofluorescence tests for the diagnosis of VZV infections,^{3,4} but none have been evaluated for the differential diagnosis of HZO.

We report the development of an immunofluorescence test for the serodiagnosis of HZO using a single sample.

Patients, Materials, and methods

PATIENTS

Sera were collected from patients attending the Zoster Clinic and Keratoconjunctivitis Clinic at Moorfields Eye Hospital in London and stored at -20°C until examined. A total of 350 sera were collected from patients with HZO, ocular HSV, and other ocular viral infections. All the sera were examined for anti-VZV IgG antibody. IgM was determined only in the sera from HZO patients. In addition, anti-HSV 1 IgG titre were determined in a subsample of sera from the HZO patients by means of a microimmunofluorescence test.⁵

Materials and methods

Antigen preparation. A strain of VZV isolated from a case of chicken-pox (kindly supplied by the Virology Department, Institute of Child Health, London) was serially passaged in HeLa cells for antigen preparation. The infected monolayers prepared in flasks were trypsinised and resuspended in growth medium. The total number of HeLa cells per ml of growth medium was adjusted to approximately 60 000 per ml of growth medium. 0.2 ml of this suspension, which contained sufficient numbers of VZV infected cells to give 50–100 VZV plaques per monolayer (Fig. 1), was placed in each of 10 wells of the Belco Micro-Slide culture chamber (A R Horwell Ltd) and the chambers incubated for 48 hours at 35°C . The monolayers were fixed with acetone for 10 minutes at

room temperature. The fixed slides were stored at -20°C until used. The stability of the antigen under these conditions of storage was satisfactory for up to three months.

Immunofluorescence test. Doubling dilutions of the sera ranging from 1 in 8 to 1 in 4096 were prepared in phosphate buffered saline (PBS) at pH 7.3. The dilutions initially examined for the presence of IgG were from 1 in 16 to 1 in 512. The presence of IgM was screened at a dilution of 1 in 8. Further higher dilutions were tested when required.

Approximately 10 μl of each of the dilutions was spread on appropriate monolayers on the slide and incubated at 37°C in a moist chamber for 30 minutes. The slides were washed in PBS for 15 minutes in a magnetic stirrer. The monolayers were air dried and covered with appropriately diluted antihuman IgG or IgM conjugated with fluorescein isothiocyanate (Hyland Laboratories Ltd, Lorne Laboratories Ltd). Incubation and washing were repeated as before except for an extra final wash of the slides in distilled water for 5 minutes. The slides were air dried and mounted in a glycerol mountant⁶ and examined with a Zeiss Standard 18UV microscope fitted with a Zeiss filter set 10. The tests were read under a $\times 16$ Neofluar objective and $\times 10$ eyepieces.

The end point of the titration was taken as the last dilution in which cells with specific fluorescence could be clearly seen.

Reproducibility of the test. The reproducibility of the test was determined by testing aliquots of two positive sera stored at -20°C on five separate occasions.

Results

Reproducibility of the test. The results showed complete agreement in titre in four of the five aliquots for each of the two sera tested. The remaining aliquot showed only a one-tube difference in titre (Table 1).

Levels of distribution of anti-VZV IgG. The distribution and levels of anti-VZV IgG in the sera of all the categories of patients are shown in Table 2. The

Table 1 Reproducibility of the immunofluorescence test: five aliquots of two positive sera tested on five separate occasions

Aliquots of sera	Anti-VZV IgG titres	
	Serum 1	Serum 2
1	16	512
2	16	512
3	16	1024
4	32	512
5	16	512

Table 2 Distribution of levels of anti-VZV IgG in the different patient groups

Clinical diagnosis	Number of sera							Total
	Anti-VZV IgG titres							
	≤16	32	64	128	256	512	≥1024	
HZO	9	4	4	10	26	46	35	134
HSV ocular	15	4	2	0	0	0	0	21
Adenovirus ocular	84	18	15	7	0	0	0	124
Other 'viral' ocular	46	9	12	2	0	2	0	71

Table 1 *Pneumatograph readings on 12 rabbits treated with subconjunctival RU486 suspension in one eye, the fellow eye being treated with 'vehicle' subconjunctivally. For weeks I to V the weekly totals of (vehicle minus RU486) differences are presented for each rabbit, with a column of mean differences per reading and per week. (Vehicle - RU486) means difference in pressure between vehicle treated (or placebo treated) and RU486 treated. Row I shows the differences between R-L or L-R depending on which eye is to be treated in weeks II to V, while rows II to V show differences between vehicle treated and actively treated eyes. Student's *t* and *p* values are placed in the end columns. Wilcoxon matched pairs signed ranks tests gave similar results in week IV ($R_- = 1 + 4.5 + 6.5 = 12$, $p < 0.10$, $n = 11$ non-zero pairs) and in week V (5 days) ($R_- = 1 + 2.5 + 4 = 7.5$, $p < 0.05$, $n = 11$ non-zero pairs)*

Week (6 days)	Rabbit												Mean diff (vehicle - RU486) per reading mmHg	Mean diff (vehicle - RU486) per week mmHg	Student's <i>t</i> (<i>n</i> =11)	<i>p</i> (NS=not significant)
	A	B	C	D	E	F	G	H	I	J	K	L				
I (Pretreat- ment)	-4	11	51	97	-58	18	-14	107	10	-79	-48	-92	-0.03	-1.0		NS
II	23	26	12	68	16	-13	37	88	105	-18	-17	-63	0.61	22	1.59	NS
III	33	17	41	104	0	-22	67	102	32	-81	11	-31	0.63	22.8	1.47	NS
IV	45	-30	95	47	21	-43	43	54	30	0	12	-10	0.61	22.0	1.96	0.07
V (5 days)	20	12	60	38	83	-16	0	43	49	-8	21	-12	0.81	24.2	2.69	0.025
I-IV	-49	41	-44	50	-79	61	-57	53	-20	-79	-60	-22		-22.1	-1.35	NS
I-V	-19	3	-5	50	-143	44	-10	55	-52	-51	-66	-71		-22.1	-1.31	NS

It was surprising that intraperitoneal waterloading with distilled water did not show any intereye difference. We had expected it would be greater than the difference found during the five weeks of treatment.

Calibration of the pneumatograph machine was done on several enucleated eyes of rabbits. Actual

pressure was monitored by a pressure transducer and chart-recorded via a needle in the anterior chamber. The readings gave very similar estimates to those of the electronic pressure transducer (but see Hammond and Bhattacharjee¹⁰).

Some contributions to variance came from lack of

Table 2 *Summary of four experiments: mean (vehicle - RU486) difference per reading*

Number of rabbits Tonometer RU-administration		12 Applanation Eye drops	12 PTG Eye drops	6 PTG Eye drops	12 PTG Sub-conjunctival injection Yamanashi (present paper)	Summed
Place		Edinburgh ⁹	Augusta I ¹⁰	Augusta II		
First treatment	Mean	0.24	0.22	0.26	0.62	1.34
Two weeks	Variance of mean	0.0245	0.0744	0.0386	0.1450	0.2824
						$z = 2.52$ $p = 0.03$
Second treatment	Mean	0.66	1.06	0.28	0.70	2.70
Two weeks	Variance of mean	0.0198	0.1252	0.0604	0.0759	0.2814
						$z = 5.09$ $p < 0.001$
Third treatment	Mean	0.69	0.39	0.84	—	1.92
two weeks	Variance of mean	0.0261	0.1342	0.0136	—	0.1739
	<i>n</i>	10*	12	5	—	$z = 4.84$ $p < 0.001$
Fourth treatment	Mean	1.03	0.38	—	—	1.41
two weeks	Variance of mean	0.0158	0.0546	—	—	0.0703
	<i>n</i>	6*	12	—	—	$z = 5.32$ $p < 0.001$
Fifth treatment	Mean	0.46	0.06	—	—	0.52
two weeks	Variance of mean	0.0280	0.1134	—	—	0.1414
	<i>n</i>	12	12	—	—	$z = 1.40$

* Incomplete tonometrist's annual leave.

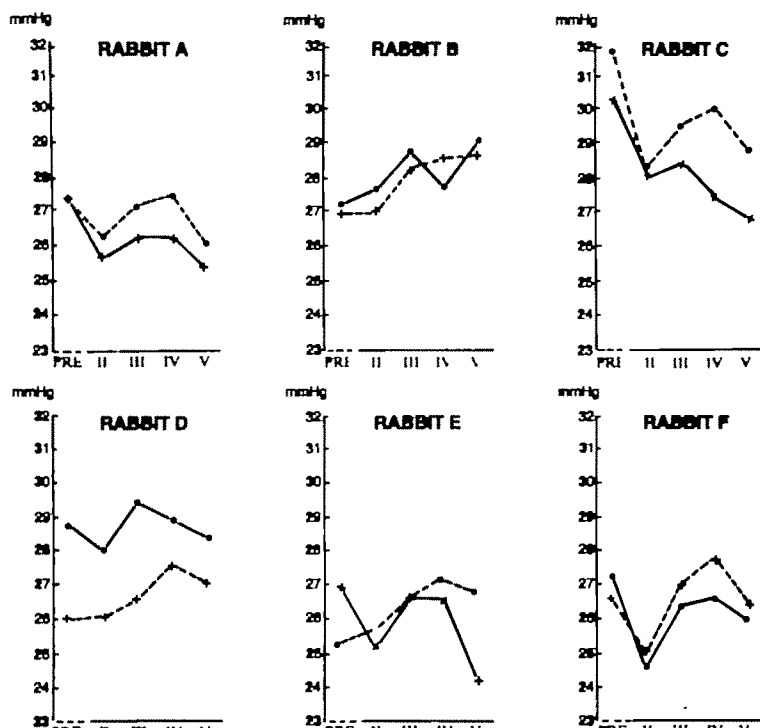


Fig. 1A

Fig. 1 Weekly mean of two daily tonometry readings for 12 rabbits given subconjunctival 2 mg of RU486 as a 1% suspension in 0.2 ml saline to one eye (+). The fellow eye received subconjunctival 0.2 ml of saline only (-). Six right eyes (—) and six left (---) received active injections.

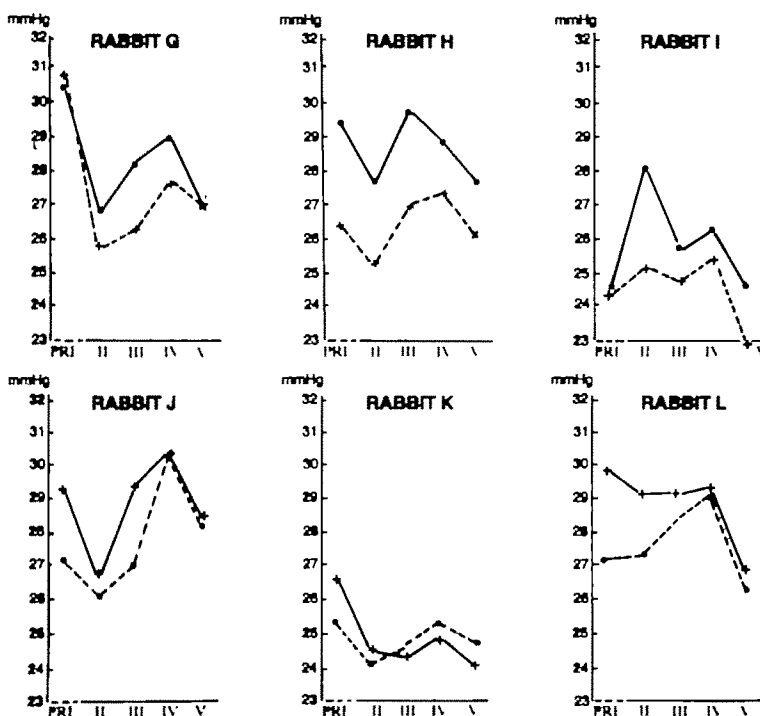


Fig. 1B

the pneumatonograph to warm up before each series of tonometries.

The 12 rabbits received twice weekly (on a Monday and Thursday, after all tonometries had been done for that day) a subconjunctival injection of 0.2 ml of a 1% suspension of RU486 (2 mg) in normal saline in one eye chosen at random; the other eye received a subconjunctival injection of the same volume of vehicle, namely normal saline only. Topical anaesthesia was obtained in all eyes by instillation of 0.4% benoxinate oxybuprocaine HCl eye drops just before the injections. Six rabbits received 'active' injections in right eyes and six in left eyes (fellow eyes having vehicle injections) to ensure that half of the actively treated eyes were tonometrised first and half of the vehicle treated eyes were tonometrised first (the right eye always being tonometrised first). That plan was used in order to avoid the possible 'contaminant' of a systematic difference in pressure between first- and second-tonometrised eyes.

Each tonometry reading was the average of three separate applications in quick succession of the pneumatonograph footplate to the cornea. Each of the three constituent pressures was read from the graph printout on the recording section of the pneumatonograph. A judgment was made of the pressure from the 5-second trace, which usually showed a gradually falling, irregular line; the judge (ST) was unbiased because he was unaware of which eye was the treated eye and which the control.

Tonometry was done twice daily, for six days per week, except for week V, which was of five days only.

Within 48 hours of the end of the series of tonometries done throughout the five treatment weeks a water loading test by intraperitoneal injections of sterile distilled water (50 ml/kg body weight) was done on each rabbit, followed by tonometry at 15-minute intervals for 1.5 hours.¹²

Results

The graphs in Fig. 1A, B show the mean tonometry for each of the 5 weeks, the first being pretreatment weeks and II to V being treatment weeks. Weeks I to IV were six-day weeks (Tuesday until following Monday), but week V was a five-day week (Tuesday to Saturday).

Table 1 shows that the mean reduction in pressure in the actively treated eye compared with the vehicle-treated eye for weeks I (pretreatment), II, III, IV, and V was -0.03, 0.61, 0.63, 0.61, and 0.81 mmHg respectively. Although these figures are quite consistent, only the reductions in weeks IV and V were significant (the reduction in week IV at the rather weak 7% significance level), because of a higher variance in weeks II and III.

Pretreatment week I was available. R-L or L-R differences are recorded in row I of Table 1 depending on whether R or L eye was planned to be actively treated in weeks II to V. Subtraction of the differences (vehicle-treated minus RU486-treated) in weeks IV and V from the differences (R-L or L-R) in pretreatment week I removed possible systematic differences between the two eyes of each rabbit but resulted in non-significant Student's *t* values (see lowest two rows of Table 1). We would attribute this to the higher variance in week I, which was a run-in week to habituate the rabbits to handling and tonometry. (Accordingly, such a week is often unsatisfactory as a *base line* 'control' week.)

Within 48 hours of the end of the series of tonometries the ocular hypertensive response to intraperitoneal injections of sterile distilled water was measured, but no intereye difference could be detected.

Discussion

The effect on IOP of subconjunctival injections of RU486, a peripheral corticosteroid blocking drug, is quantitatively very similar to that of eye drops which has already been reported,⁹ when the ocular tension also fell by about 0.75 mmHg. The initiating hypothesis in both series has been that one factor normally affecting (reducing) the facility of outflow of aqueous humour is the effect of normal tissue levels of corticosteroids. We have not yet been able to do clinical trials of eye drops which we expect would produce a greater fall in pressure in patients with or hereditarily predisposed to open-angle glaucoma, because their trabecular meshwork is probably more susceptible to normal tissue steroid levels than is the normal meshwork. The rabbit eye is by no means ideal for these studies but has the material advantage of inexpensive convenience, and also does respond to corticosteroid drops with a rise in pressure, albeit transient.^{13,14}

It was rather disappointing to find that the subconjunctival route may not be more effective than the route via eye drops, but we are cautious about overinterpreting intertrial similarities. A possible explanation may lie in the insolubility of RU486 in water. However, a plausible explanation is that the subconjunctival route merely constitutes a reservoir to supply a continuous stream of any drug through the puncture wound of the conjunctiva and over the cornea through which the drug is absorbed; an interesting paper by Wine *et al.*¹⁵ provides good evidence for that mechanism of action. We could not accurately assess the depth of the injection; a subconjunctival level seems to achieve better penetration than a sub-Tenon's level.^{16,17}

Subconjunctival suspension of RU486 lowers intraocular pressure in normal rabbits

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SUMMARY RU486 is both a progesterone blocker and a corticosteroid blocker (peripheral). Subconjunctival injections of 0.2 ml of a 1% suspension of RU486 powder (2 mg) were given twice weekly to one eye chosen at random of 12 rabbits. The fellow eye received the same volume, 0.2 ml, of vehicle (normal saline) only. Ocular tension was measured twice daily for six days per week by an Alcon pneumatograph, the tonometrist(s) being unaware of which eyes were treated and which untreated. A small but significant reduction in intraocular pressure, about 0.7 mmHg, occurred in treated eyes. No intereye difference in the ocular hypertensive response to intraperitoneal injections of distilled water (50 ml/kg) was found. Clinical trials are planned in which a larger fall is expected because the trabecular meshwork in patients with open-angle glaucoma or ocular hypertension is presumably more affected by (normal) tissue levels of corticosteroid.

It is well documented that corticosteroid eye drops will cause a rise of intraocular pressure (IOP), especially in patients with open-angle glaucoma or with a hereditary predisposition to that disease.¹⁻⁸ The trabecular meshwork is presumably hypersusceptible to corticosteroids in patients who show a very high ocular hypertensive response. The appearance of a new drug, RU486, with *peripheral* corticosteroid blocking as well as progesterone blocking properties allowed preliminary rabbit experiments to test the hypothesis that such a drug would be useful in open-angle glaucoma. A series of 12 rabbits treated with a 1% suspension of eye drops in one eye chosen at random showed a small fall in pressure when compared with the fellow vehicle treated eye.⁹

RU486 has the disadvantage, at least from the point of view of treatment of the eye, of extreme insolubility in water, though it is soluble in fat and fat solvents. It seemed likely that greater intraocular penetration, and therefore a more powerful ocular hypotensive effect, could be achieved by subconjunctival injection, which is the subject of the present report.

The effect on IOP is probably due to an improved outflow of aqueous humour as judged by fluorescein decay studies also in rabbits.¹⁰ That in turn is presumed to be due to a peripheral blocking effect on the normal tissue level of corticosteroid in the outflow channels. The effect may, however, be the result of the drug's peripheral progesterone blocking effect, which also accounts for its powerful contraceptive (abortifacient) properties.¹¹

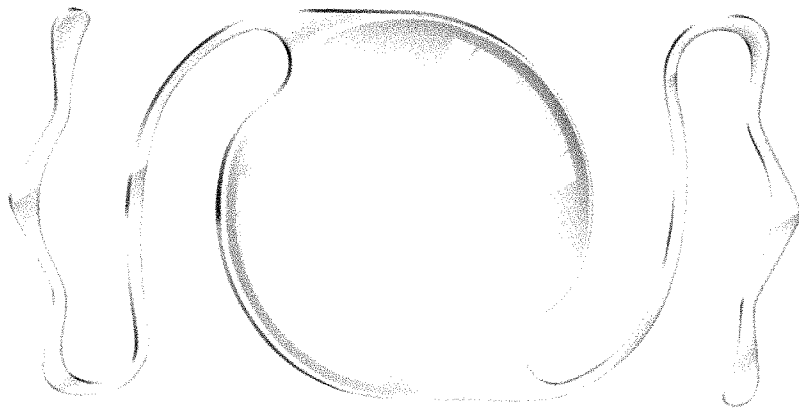
Material and methods

Six New Zealand black and white and six albino rabbits (A to L) were allowed to settle down in the animal house for one week before the study began. After that, tonometry was done twice daily at about 0830 and 1700 h for one week without treatment (run-in week). This allowed the rabbits to become used to tonometry and the tonometrist and assistants to become more practised with the Alcon pneumatograph.

Almost all applications of the tonometer to the rabbits' eyes were done by one experienced tonometrist (TS); the extremely few exceptions were unavoidable. The right eye was invariably assessed first, the left second. Fifteen minutes was allowed for

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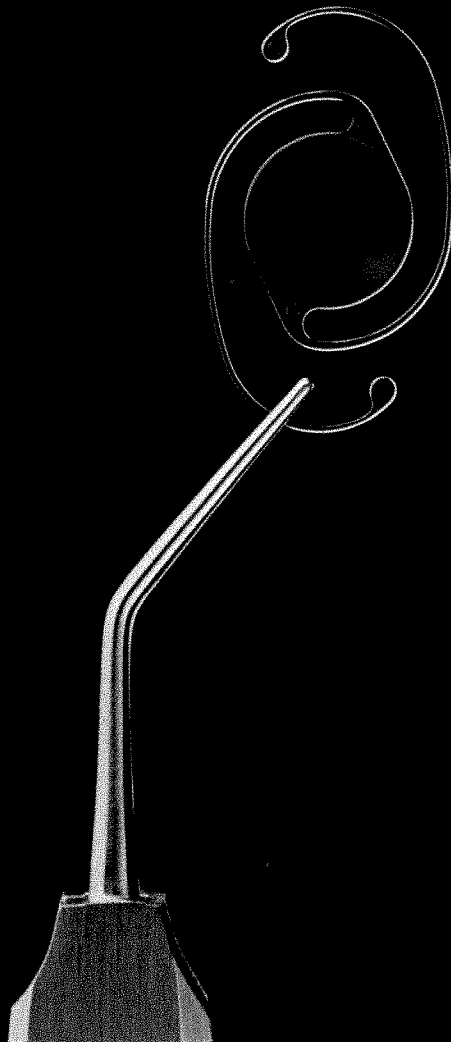
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Pupil size, visual acuity, brachial artery blood pressure, and pulse rate were unchanged over the test period.

Discussion

We wished to answer the question of whether dopamine receptor blocking drugs are effective in reducing human intraocular pressure. We chose haloperidol because it is more effective in reducing cat IOP than other dopamine blocking drugs.⁶ In addition there is long clinical experience with the use of systemic haloperidol.

Studies in experimental animals have shown an impressive ocular hypotensive effect (30% decrease in IOP) after topical haloperidol application, and it has been suggested that these drugs may be an effective treatment for glaucoma.⁶ We believe that this is the first time topical haloperidol has been tested in humans. Our results show that haloperidol produces a small reduction in IOP at 2 hours which was not statistically significant for the numbers tested. Topical haloperidol is therefore not likely to be a clinically useful agent in the treatment of patients with glaucoma.

Several factors may have contributed to the discrepancy between our results and those from animal work. In our patients haloperidol was instilled after corneal sensation had returned. Stinging was a feature of haloperidol instillation, and reflex hypersecretion may have washed the drug off the ocular surface. In a study of aqueous humour dynamics Chiou⁷ instilled haloperidol at time 0, contemporaneously with tonometry. These cats were anaesthetised with pentobarbital, and this may have prevented reflex tearing. Further, these eyes had indwelling cannulae at the time of eyedrop application, which may have artefactually increased drug penetration into the anterior chamber. Chiou's studies used the time taken to return to normal IOP after intravenous infusion of hypertonic saline as an index of rabbit aqueous humour secretion.^{3,6-8} It is possible that the mechanisms involved in the aqueous secretory response of the hyperosmolar experimental animal may differ from those maintaining physiological IOPs in humans. Finally, the question arises whether the laboratory animal and the human patient differ in their IOP pharmacology. Other workers have noted that the effect of timolol is less marked in experi-

mental animals^{2,9,10} than in humans.¹¹ This may account for the differences between haloperidol and timolol in Chiou's studies.^{7,8}

Chiou⁷ showed that haloperidol acts by increasing aqueous humour outflow and reducing aqueous humour production. Although most effective glaucoma treatments still reduce normal IOPs by 25-30%, it is possible that dopamine receptor blockers may have a greater effect in patients with glaucoma or raised IOPs. These factors may explain the discrepancies between results in human volunteers and animals.

In conclusion we find that a study of the use of haloperidol in normal human volunteers does not support a role for haloperidol as an effective glaucoma treatment. Caution is required in extrapolating results from experimental animals to humans.

We thank the medical, paramedical, and nursing staff at the Western Ophthalmic Hospital for volunteering for this study. We thank Mr Redmond Smith for advice and encouragement.

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Table 1 Mean percentage intraocular pressure differences from base line pressures

Preparation	% Difference at 2 hours		% Difference at 4 hours		% Difference at 6 hours	
	Active	Placebo	Active	Placebo	Active	Placebo
1% Eye drops (13 subjects)	-9.55 (± 10.01)	-3.55 (± 8.12)	-9.84 (± 13.08)	-4.99 (± 10.57)	-6.19 (± 11.77)	-8.06 (± 11.44)
t Test values for paired differences	1.68		1.0		0.41	
0.125% Eye drops (7 subjects)	-15.04 (± 16.53)	-3.73 (± 11.22)	-1.93 (± 10.63)	-5.87 (± 18.50)	-8.1 (± 14.50)	2.72 (± 10.90)
t Test values for paired differences	1.5		0.32		1.33	
Total mean % differences (20 subjects)	-11.47 (± 12.52)	-3.61 (± 9.02)	-8.26 (± 12.70)	-5.17 (± 11.70)	-6.72 (± 12.16)	-5.07 (± 12.04)

Results given $\pm$ one standard deviation. Results not significant at the 5% level ($t < 1.96$)

pulse rate were measured at base line and at two and six hours after topical haloperidol. A full slit-lamp examination was performed before each IOP measurement, and subjects were questioned about ocular symptoms.

Volunteers were excluded from the study if there was any known or detected ocular disease, if any topical medication was in use, or if systemic beta adrenergic or dopamine receptor blocking agents were taken.

Results

Haloperidol produced a small reduction in IOP, with a maximum reduction of 11.4% at 2 hours. The mean reduction from baseline IOP in control eyes was 3.9% at 2 hours. Thereafter the difference between test and control eyes diminished (Fig. 1). The

difference was not significant at $p < 0.05$ for the numbers tested. The ocular hypotensive effect of haloperidol was of small magnitude and short duration (Table 1).

Stinging was noted by all subjects and was of sufficient intensity to induce reflex lacrimation in most of them.

A fine punctate epithelial keratitis (PEK) developed in the lower half of both test and control eyes in 50% of subjects.¹⁰ The signs resolved within a few hours and were attributed to benoxinate induced epithelial toxicity.

However two of these 10 had PEK more marked on the test eye, and a further four subjects developed lower half PEK in the test eye only, with no signs on the control eye. Thus the haloperidol/lactic acid solution may have an element of acute epithelial toxicity which is mild and of short duration.

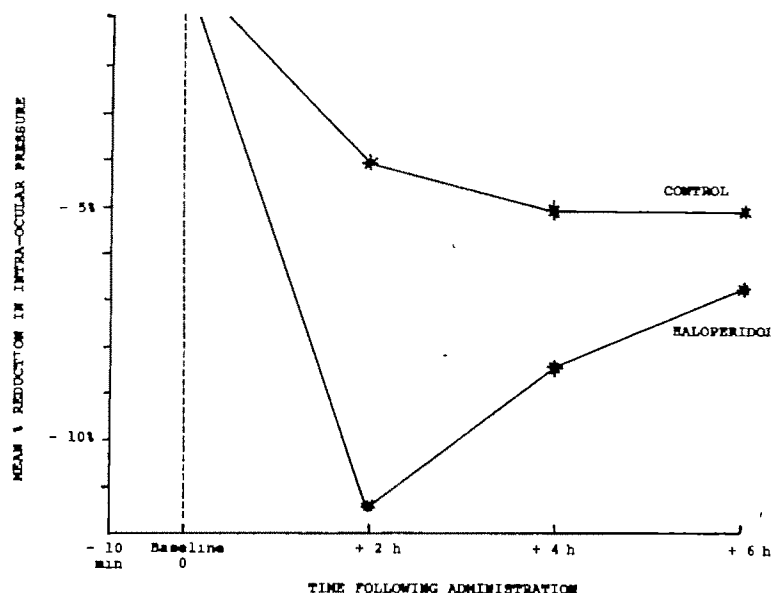


Fig. 1 Mean percentage reduction in IOP following topical haloperidol instillation

Is topical haloperidol a useful glaucoma treatment?

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SUMMARY A randomised, double blind, single dose study of topical haloperidol, a dopamine receptor blocking drug, was performed on 20 healthy volunteers. After its administration a modest reduction in intraocular pressure was recorded over the six-hour study period, but the difference was not significant at the $p < 0.05$ level. Although dopamine blocking agents are effective in reducing intraocular pressure in experimental animals, topical haloperidol appears unlikely to be clinically useful in the treatment of glaucoma.

We were stimulated to examine the effect of topical haloperidol, a dopamine receptor blocking drug, on human intraocular pressure (IOP) as a result of recent work regarding timolol's mechanism of action. Topical timolol is widely used in the treatment of glaucoma but is contraindicated in patients with cardiovascular or respiratory disease, as it may precipitate serious, occasionally fatal, side effects.¹ Timolol's major side effects are the result of beta adrenergic blockade.¹ However, there is evidence that its inhibitory effect on aqueous humour secretion may not be a result of beta adrenergic blockade²⁻⁵ but of dopamine receptor blockade.⁵⁻⁸

Timolol's action may not be mediated by beta receptors, since its binding to ocular beta receptors is short lived, though its ocular hypotensive action is long lasting.² Natural beta receptors are orientated in favour of the L-isomer, so that D-timolol has only 3% of the systemic beta blocking action of L-timolol. However, D-timolol is as effective as the L isomer in reducing intraocular pressure (IOP) when infused into the cat eye.³ In addition timolol lowers intraocular pressure (IOP) in patients with third neuron Horner's syndrome, that is, in the absence of ocular sympathetic innervation.⁴

Timolol may act in part on dopamine receptors, since it reduces the concentration of dopamine in the iris and ciliary body but leaves adrenaline, nor-adrenaline, and prostaglandin levels unaffected.⁵

In animal experiments studying the recovery time of the IOP after intravenous infusion of hypertonic saline, topical dopamine increased the IOP while

timolol reduced it. The effect of timolol was neutralised by simultaneous dopamine administration.⁶ In this experimental model topical haloperidol, a dopamine antagonist, reduces the IOP more profoundly and for a longer duration than timolol.^{7,8}

Since there is a need for a long acting topical ocular hypotensive agent with no beta adrenergic blocking effects, we performed a single drop, double blind study of topical haloperidol in human volunteers.

Subjects and methods

This study was approved by the Ethics Committee of St Mary's Hospital. Twenty healthy subjects volunteered, and informed consent was obtained from all.

Sterile, viscous solutions of haloperidol 0.125% or haloperidol 1.0% in water containing 0.5% or 0.7% lactic acid respectively were prepared and found to have a pH 5.5.

Intraocular pressures were measured with a Goldmann applanation tonometer which was standardised before and after each test session. The same instrument was used throughout the study. The IOPs were measured after instilling topical benoxinate and fluorescein: 10 minutes before application of topical haloperidol and at two, four, and six hours after. Eye drops were instilled independently by trained ophthalmic nurses.

The first seven subjects received haloperidol 0.125%, while all others received haloperidol 1.0%. Saline or inert vehicle was applied to the control eyes. Test eyes were randomised, and the study was performed in a double blind fashion.

Visual acuities, brachial artery blood pressure, and

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The subjective relief of the most frequently presented symptom, grittiness,⁴ was alleviated immediately and lasted up to 60 minutes. Grittiness was significantly reduced only on intragroup analysis (Fig. 2, Table 2). Similarly burning was also alleviated. This relief persisted for up to 60 minutes, and it was also significant on intragroup comparison (Fig. 3, Table 3). Pollack and McNiece²² showed that the relief of 'pain', a chronic symptom, at least in the severe dry eyes was obtained only after prolonged use of sodium hyaluronate.

In this 'acute' study itchiness and photosensitivity failed to respond to the treatment with sodium hyaluronate.

In conclusion it has been shown, both objectively and subjectively, that 0.1% sodium hyaluronate (unpreserved) could have a role in the management of dry eyes. The beneficial effect of sodium hyaluronate is most likely attributed to its viscoelastic properties, which are akin to those of natural tears.

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Table 1 Inter- and intragroup comparison of NIBUT in control (0.9% saline) and test (0.1% sodium hyaluronate) dry eyes

Test	Control (min)	Baseline	+1	+5	+10	+20	+40	+60
Baseline	NS	NS	NS	NS	NS	NS	NS	NS
+1		0.0001	0.004					
+5		0.00001		0.04				
+10		0.00001			0.003			
+20		0.0003				0.049		
+40		0.01					0.047	
+60		NS						NS

NS = not significant ($p > 0.05$).

Diagonal values indicates intergroup comparison. Horizontal and vertical values indicates intragroup comparison.

Table 2 Inter- and intragroup comparison of subjective score of grittiness in control (0.9% saline) and test (0.1% sodium hyaluronate) dry eyes

Test	Control (min)	Baseline	+10	+40	+60
Baseline		NS	NS	NS	NS
+10		0.01	NS	NS	NS
+40		0.03		NS	NS
+60		0.01			NS

NS = not significant ($p > 0.05$).

Diagonal values indicates intergroup comparison. Horizontal and vertical values indicates intragroup comparison.

Table 3 Inter- and intragroup comparison of subjective score of burning in control (0.9% saline) and test (0.1% sodium hyaluronate) dry eyes

Test	Control (min)	Baseline	+10	+40	+60
Baseline		NS	NS	NS	NS
+10		0.01	NS	NS	NS
+40		0.03		NS	NS
+60		0.05			NS

NS = not significant ($p > 0.05$).

Diagonal values indicates intergroup comparison. Horizontal and vertical values indicates intragroup comparison.

The symptoms score were assessed at +10, +40, and +60 minutes following treatment.

Results

The frequency distribution in the non-invasive break-up time and the subjective scores of grittiness and burning are shown in Figs. 1 to 3. The data was analysed by the non-parametric Mann-Whitney U test for both inter- and intragroup variations of the test and control eyes. The results are presented in Tables 1 to 3.

The baseline distribution of the NIBUT in the

control and test eyes is shown in Fig. 1. In the control eyes 55% of the NIBUT measurements were in the 0–9 seconds interval, 20% were in each of the 10–19 and 20–29 seconds intervals. Only 5% of the NIBUT were greater than 30 seconds. In the test eyes 70% of the NIBUT values were in the 0–9 seconds interval and 30% in the 10–19 seconds interval. None of the values were greater than 30 seconds. These baseline distributions were not significantly different ($p > 0.05$).

After instillation of a drop of 0.1% sodium hyaluronate there was a significant increase in tear film stability at one minute in comparison with normal saline ($p < 0.05$; Fig. 1C, D; Table 1). This stabilising effect persisted for at least 40 minutes ($p < 0.05$; Fig. 1; Table 1). Sodium hyaluronate treated eyes showed, over their baseline readings, a highly significant increase in the NIBUT ($p = 0.0001$ at 1 minute, $p = 0.01$ at 40 minutes; Table 1) as well.

Figs. 2 and 3 show frequency distributions of subjective scores for the following symptoms: (i) grittiness (Fig. 2); (ii) burning (Fig. 3).

Fig. 2 represents the variations in the scores of grittiness, which were not significantly different ($p > 0.05$; Table 2). After treatment with sodium hyaluronate there was an immediate relief of grittiness, which lasted for 60 minutes. Table 2 shows the inter- and intragroup significance levels for both the test and the control eyes.

Fig. 3 shows the variation in score for 'burning'. These base line distributions were comparable ($p > 0.05$). On treatment with sodium hyaluronate there was a significant relief from burning, which was present at 10 minutes ($p = 0.01$), 40 minutes ($p = 0.03$), and 60 minutes ($p = 0.05$); Table 3).

The frequency distributions of the symptom scores for itchiness and photosensitivity before and after treatment are omitted, as the symptoms were not significantly alleviated ($p > 0.05$).

Discussion

Sodium hyaluronate unlike other available tear substitutes is a non-newtonian fluid which shear thins and rapidly regains its original viscosity (Kaura R, Tiffany JM, unpublished; Pharmacia, personal communication, 1985). It has been shown to adhere to corneal epithelium, and thus it is useful in the management of patients with severe dry eye.²

In this study the NIBUT and symptoms were used as criteria to assess the usefulness of 0.1% sodium hyaluronate (unpreserved) in the treatment of keratoconjunctivitis sicca. The topical application of 0.1% sodium hyaluronate significantly increased the NIBUT in comparison with the control eye (saline treated) for up to at least 40 minutes (Fig. 1, Table 1).

was rigidly adhered to throughout the study.

The study began by one drop of either sodium hyaluronate (0.1%) or sodium chloride (0.9%) being placed in the lower fornix temporally in the test and control eye[®] with a minimum of delay between drop installations. The patient blinked in order to mix the applied drop with the conjunctival fluid.

Measurement of NIBUT began one minute after the last drop. The patient while positioned at the

instrument was requested to make a complete unforced blink. The time taken in seconds between the last complete blink and the appearance of the first randomly located break(s) in the reflected grid pattern was taken to be the NIBUT. If the tear film remained intact for 30 seconds or longer, the reading was terminated.

The tear film stability was assessed at the following times: +1, +5, +10, +20, +40, and +60 minutes.

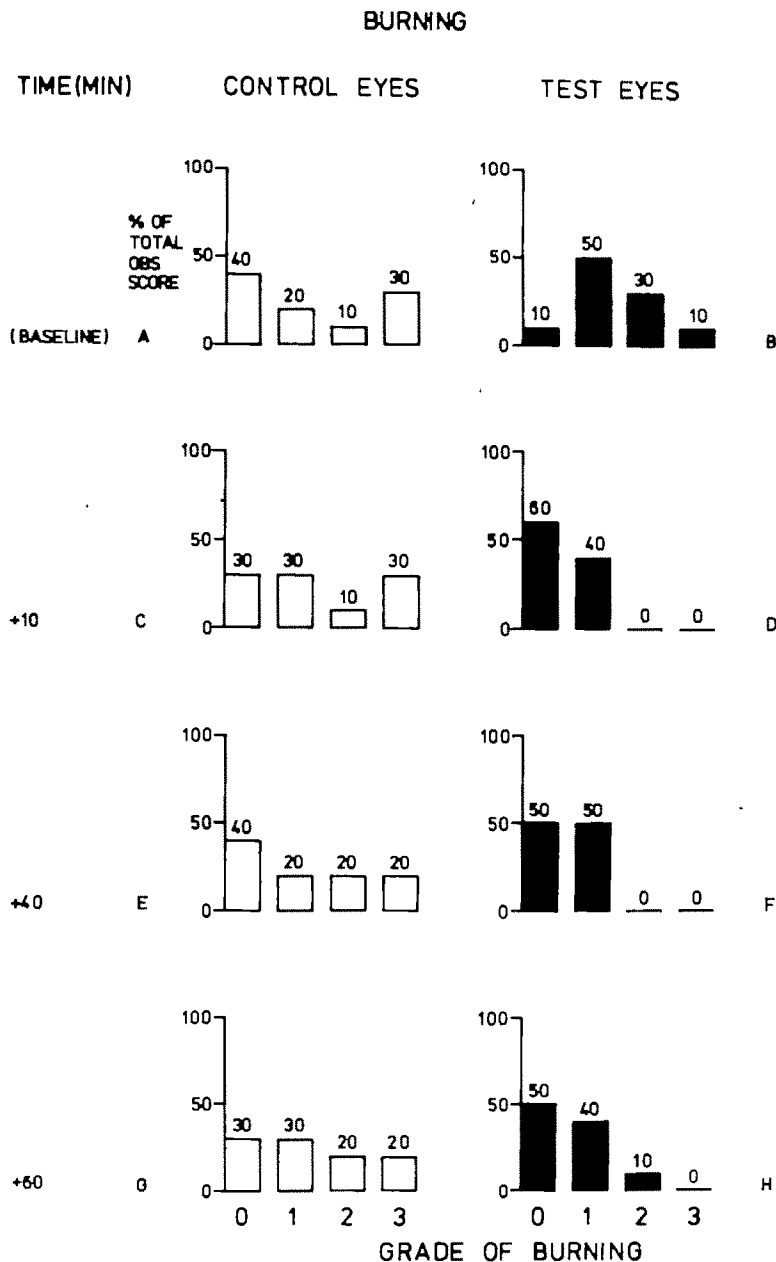


Fig. 3 Frequency distribution of burning in the control and test eyes before and after treatment.

0.1% Sodium hyaluronate tears were prepared by injecting 1.2 ml of 1% proprietary Healonid into 10.8 ml of unpreserved balanced salt solution, in a laminar flow cabinet.

Prior to treatment, subjective symptoms of grittiness, burning, itching, and photosensitivity for each eye at the time of assessment were recorded on a 0 to +3 scale (0=absent, +1=mild, +2=moderate, and +3=severe) by one of the investigators.

The precorneal tear film stability (NIBUT) was measured by a non-invasive instrument which avoids the use of fluorescein.¹⁴ All observations were made in a masked manner by a separate observer uninvolved with drop instillation and history taking. The NIBUT was determined twice for each eye, alternating between eyes for each measurement. The eye having its NIBUT assessed first was randomly chosen, but for a given patient the sequence of testing

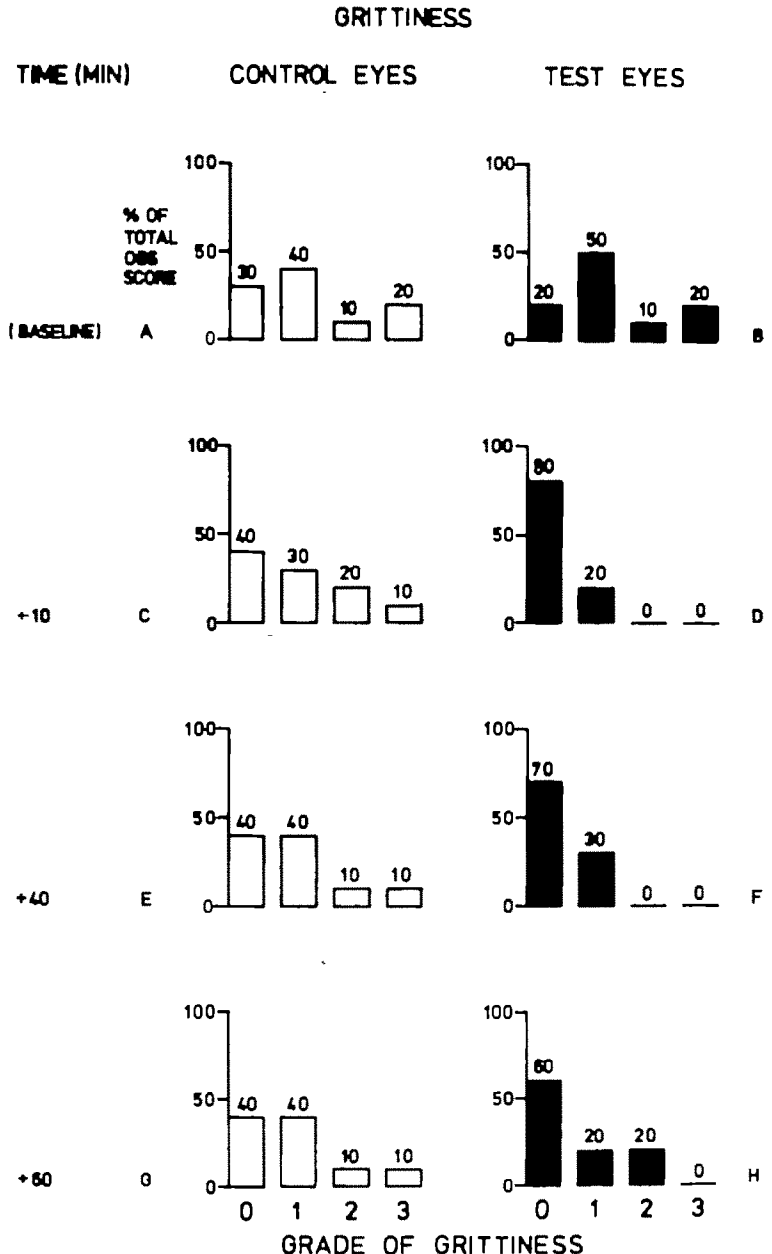


Fig 2 Frequency distribution of the grittiness in the control and test eyes before and after treatment.

one eye had 6 mm, and the remaining eye had 8 mm of wetting in 5 minutes; a typical staining pattern with fluorescein and a non-invasive tear film break-up time (NIBUT) of less than 30 seconds were observed in the least affected eye. We excluded dry eye patients with a history of other ocular disease, past anterior segment surgery, iritis, contact lens wearers, and those on topical therapy other than artificial tears.

The participants were requested not to use their existing artificial tears at least 12 hours prior to their appointment. One eye of each patient was randomly chosen to receive one drop of unpreserved sodium hyaluronate (0.1%), this being the test eye. The fellow eye received one drop of unpreserved sodium chloride (0.9% saline), this being the control eye. Both the solutions were dispensed from identical dropper bottles labelled A and B.

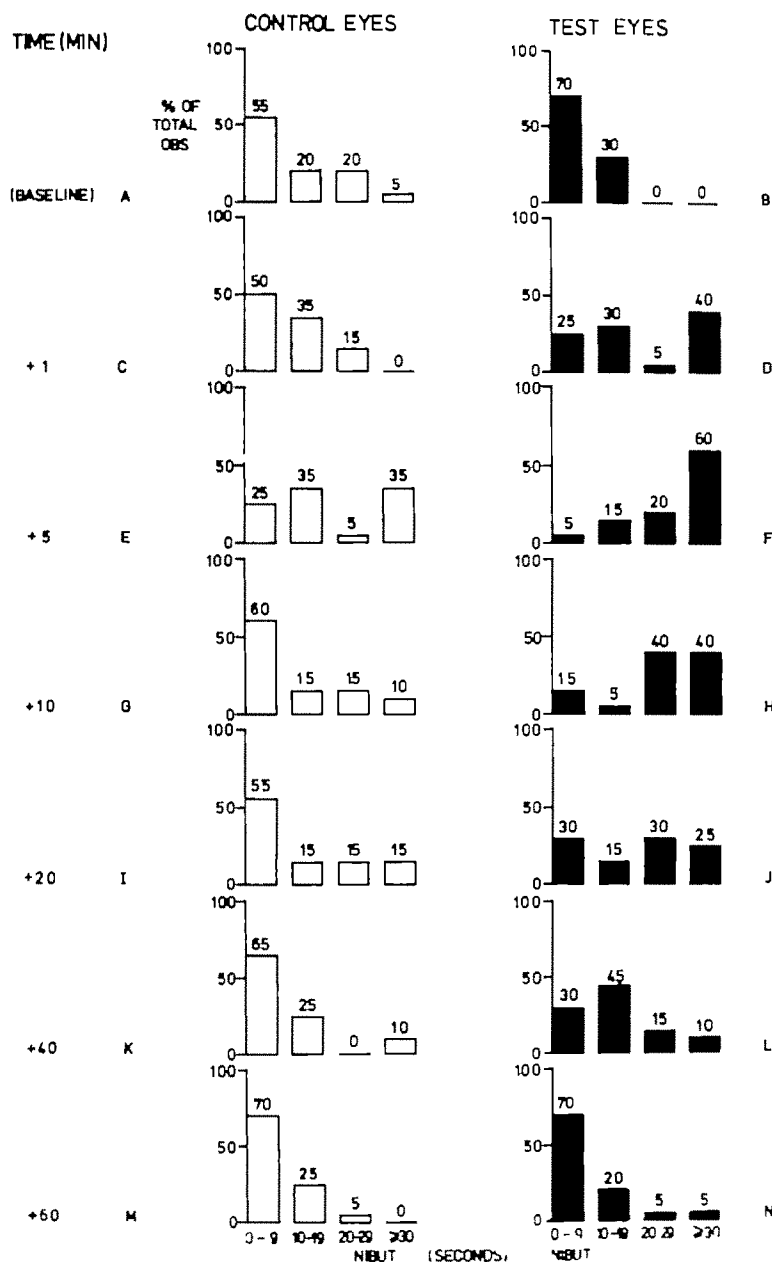


Fig. 1 Frequency distribution of the non-invasive break-up time of control and test eyes before and after treatment with normal saline and unpreserved sodium hyaluronate (0.1%)

Effect of sodium hyaluronate (0.1%) on break-up time (NIBUT) in patients with dry eyes

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SUMMARY We evaluated the effect of 0.1% sodium hyaluronate (unpreserved) in 10 patients with dry eyes. The precorneal tear film break-up time was assessed by the non-invasive technique, and the severity of symptoms was recorded before and after treatment on a 0 to +3 scale. It was found that the tear film stability was significantly increased ($p < 0.05$) in eyes treated with sodium hyaluronate. The symptoms of grittiness and burning were also significantly alleviated in the treated eyes.

Dry eyes may be caused by inadequacy of one or more of the major tear fluid components. Causes include deficiency of meibomian lipid, aqueous fluid, and mucus glycoprotein¹⁻³ and also inadequate blinking, poor lid-globe apposition, abnormal surface elevations, and breakdown in the wettability of the conjunctival and corneal epithelial surface cells.

Dry eyes give rise to chronic ocular discomfort. Patients complain of burning, itching, photosensitivity, and grittiness. The last is the most frequent symptom in 88% of the cases.⁴ The diagnosis of dry eyes is also based on the results of a battery of clinical tests, notably Schirmer's test, tear film break-up time (BUT),⁵ vital staining with fluorescein and/or rose Bengal.⁵⁻⁶ In recent years a number of other tests such as thread Schirmer's,⁸ kinetic wetting,⁹ osmolarity,¹⁰ cytology of ocular surface,¹¹ and contact specular microscopy¹² have been added. Haematological investigations, for example autoantibodies, are also conducted to distinguish between primary and secondary Sjögren's syndrome.^{13,14} The mainstay of dry eye treatment is tear supplementation with solutions containing hydrophilic polymers such as substituted methyl ethers or cellulose, polyvinyl alcohol, or polyvinylpyrrolidone. These solutions lubricate the eye during blinking and prevent the eye from drying when open.¹⁵

The efficiency of tear substitutes is measured by relief of symptoms, decrease in tear film BUT, decrease in fluorescein and rose Bengal staining intensity, and improvement in Schirmer paper

wetting.¹⁶ Since stability of the tear film is thought to contribute to the relief of symptoms, break-up time provides the simplest short-term index of efficiency. However, the conventional break-up time test is invasive and requires the instillation of fluorescein, which has been shown itself to shorten the break-up time.¹⁷ Fluorescein could also modify the effect of the drop being investigated. Since repeated measurements of stability are required to assess the efficacy of the drop over a time interval, the non-invasive technique provides an alternative method without the use of fluorescein.

Solutions of sodium hyaluronate have biophysical properties like those of mucus glycoprotein and native tears. Such solutions have non-newtonian properties and 'shear thin' at high shear rates (Kaura R, Tiffany JM, unpublished).

In this paper the efficacy of unpreserved 0.1% sodium hyaluronate is evaluated in dry eye patients in: (i) increasing the tear film stability by means of the non-invasive break-up time; (ii) alleviating ocular symptoms.

Materials and methods

Eleven dry-eye patients (7 female, age range 25-74 years; 4 male, age range 37-74 years) with a varying duration of keratoconjunctivitis sicca for between one and 40 years were recruited after informed consent from a pool of over 100 patients currently receiving treatment for dry eyes at the Oxford Eye Hospital. Ten dry-eye patients were accepted into the study. Eighteen eyes (90%) had Schirmer tear test values (without topical anaesthesia) < 5.5 mm,

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Table 1 Tear lysozyme levels in mg/ml in healthy subjects, acute adenovirus conjunctivitis, and different stages of conjunctivitis

	No. of subjects	Mean $\pm$ SD	Range
Healthy subjects	92	1.45 $\pm$ 0.60	0.32–2.85
Conjunctivitis	98	1.15 $\pm$ 0.50	0.30–2.44
Mild	28	1.36 $\pm$ 0.48	0.32–2.20
Moderate	52	1.13 $\pm$ 0.47	0.32–2.44
Severe	18	0.90 $\pm$ 0.50	0.30–1.92

SI conversion: mg/ml = g/l

Table 2 Tear lysozyme levels in mg/ml in the acute phase in viral isolation-positive and viral isolation-negative patients with acute adenovirus conjunctivitis

	No. of subjects	Mean $\pm$ SD	Range
Isolation-positive	30	1.07 $\pm$ 0.49	0.32–1.98
Isolation-negative	68	1.19 $\pm$ 0.50	0.30–2.44

SI conversion: mg/ml = g/l.

adenovirus conjunctivitis and healthy controls is given in Table 1. It was 1.49 $\pm$ 0.69 mg/ml in males and 1.41 $\pm$ 0.50 mg/ml in females and the difference in the two sexes was not significant statistically ($p > 0.80$). There was a significant decrease when the tear lysozyme level in the acute stage was compared with the level in healthy subjects ($p < 0.001$). (SI conversion: mg/ml = g/l.)

Table 1 also shows tear lysozyme levels in mild (1.36 mg/ml), moderate (1.13 mg/ml), and severe (0.90 mg/ml) types of acute adenovirus conjunctivitis. The tear lysozyme level showed a significant decrease in moderate ($p < 0.001$) and severe ($p < 0.001$) types of disease, while its level in the mild type ($p > 0.50$) remained unaltered in comparison with the levels in healthy subjects (1.45 mg/ml).

The tear lysozyme levels in patients who were viral isolation-positive and viral isolation-negative is given in Table 2. A statistically significant difference was found when the level in healthy subjects (1.45 mg/ml) was compared with the level in viral isolation-positive patients ($p < 0.01$) and viral isolation-negative patients, ($p < 0.01$). However, there was no statistically significant difference ($p > 0.3$) between the tear lysozyme level in viral isolation-positive patients (1.07 mg/ml) and viral isolation-negative patients (1.19 mg/ml).

The tear lysozyme levels were determined in 56 patients during the acute and remission stages. During the acute phase the level was 1.11 $\pm$ 0.50 mg/ml (range 0.30 to 2.20 mg/ml), and the level rose to 1.32 $\pm$ 0.44 mg/ml (range 0.37 to 2.20 mg/ml)

during remission. There was a statistically significant difference ($p < 0.02$) in the levels in the acute and remission stages. There was no significant difference ($p > 0.20$) between the tear lysozyme level in the remission stage and the level in healthy subjects.

Discussion

The tear lysozyme levels have been measured on the premise that changes in tear protein levels may reflect significant events in acute adenovirus conjunctivitis. Several studies have been reported on the tear lysozyme levels in healthy subjects.^{2,10,22} Low levels have been reported in tears from patients with trachoma² and lepromatous leprosy.¹⁰ However, tear lysozyme levels have been shown to be unaltered in acute bacterial conjunctivitis,¹¹ vernal conjunctivitis,¹¹ phlyctenular keratoconjunctivitis,¹¹ chronic irritative conjunctivitis,¹¹ and nutritional xerosis.¹¹ Tear lysozyme levels have been reported to be significantly low in patients with herpes simplex virus eye infections.⁹

It has been suggested that a low tear lysozyme level in patients with acute bacterial conjunctivitis is due to excessive tearing.¹⁰ The low level of tear lysozyme in patients with acute adenovirus conjunctivitis which we observed in this study may be partly explained by the excessive tearing frequently observed in these patients.

There is a correlation between increasing severity of the disease and the reduction in tear lysozyme level, and there is a return to normal lysozyme level during the remission stage. It is therefore likely that the low level of tear lysozyme in patients suffering from adenovirus conjunctivitis observed in the present study was due to infection and not inherent or pre-existent.

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Immunoassay of tear lysozyme in acute adenovirus conjunctivitis

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SUMMARY The tear lysozyme levels were measured by immunoassay in 92 healthy subjects and 98 patients with acute adenovirus conjunctivitis. They were found to be significantly decreased during the acute phase of the disease. The extent of this decline in the tear lysozyme level was correlated with increased severity of disease. There was no significant difference in the tear lysozyme level in viral isolation-positive and isolation-negative patients. The tear lysozyme level showed return to normal levels with clinical improvement.

Lysozyme is an easily measurable component of human tears and is of diagnostic value in certain ocular diseases.¹ Tears deficient in lysozyme have been described in Sjogren's syndrome,^{2,3} keratoconjunctivitis sicca,^{4,5} smog irritated eyes,⁶ herpes simplex viral eye infection,⁷ bacterial conjunctivitis,^{8,9} trachoma,¹⁰ lepromatous leprosy,¹¹ corneal ulcer,^{12,13} and protein calorie malnutrition.¹⁴

The tear immunoglobulin,¹⁵ serum immunoglobulin,¹⁶ and complement component¹⁷ levels have been estimated by us in patients with acute adenovirus conjunctivitis. However, tear lysozyme levels have not been studied. Here we report our observations on tear lysozyme levels in patients suffering from adenovirus conjunctivitis in the acute and remission stages. The findings on adenovirus culture and serological titres have been described elsewhere.¹⁸

Material and methods

The study was carried out among 92 healthy subjects and 98 patients with acute adenovirus conjunctivitis attending the outpatient department of Guru Nanak Eye Centre, New Delhi. The control group comprised healthy subjects who had no evidence of ocular or systemic disease and who attended the Eye Centre during the same period mainly for the purpose of refraction. In the control group were 48 males and 44 females with a mean age of 34.5 (SD 16.7) years (range 8 to 63 years) and the diseased group comprised 80 males and 18 females with mean age of 28.3 (SD 12.9) years (range 5 to 63 years). The

diagnosis of acute adenovirus conjunctivitis was established by detailed clinical examination including slit-lamp biomicroscopy, bacterial culture, viral culture, and specific serological studies. The patients were subgrouped as mild, moderate, and severe according to the intensity of chemosis and congestion. All patients from whom pathogenic bacteria were isolated from conjunctival swabs were subsequently excluded from the present study. Adenovirus types 2, 7, and 8 could be cultured only from 30 out of 98 patients, and the findings are reported elsewhere.¹⁸

Tear samples were also collected for lysozyme level analysis from 56 patients with adenovirus conjunctivitis during the stage of remission when there was no clinical evidence of the disease.

Stimulated tear samples (100 to 200 µl) were collected by the method described previously¹⁹ and stored at -20°C until assayed. The lysozyme level in tear samples was quantified by a single radial immunodiffusion technique²⁰ as modified and described previously.²¹ Monospecific rabbit antihuman lysozyme serum was obtained commercially from the Behring Institute, West Germany. The reference standard was obtained from Kallestad, USA. The level of lysozyme in tears was calculated from the calibration curve constructed by incorporating three known concentrations of reference standard for every set of lysozyme determinations. The results were statistically analysed by Student's *t* test.

Results

The tear lysozyme levels in patients with acute

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ment samples* were obtained four hours after an average of 9.4 previous doses. Samples of tear fluid from 26 patients and plasma from 27 patients were assayed (Table 2). The acyclovir concentration in tear fluid showed extreme variability, ranging from 0.34 to 2068.44 μM , believed to be due to contamination of many of the samples with the acyclovir ointment itself. Plasma acyclovir levels were all at or below the limit of detection of the assay (0.01 μM).

No serious side effects were recorded, and no patient was withdrawn from the study because of adverse effects. In four patients receiving acyclovir ointment large punctate epithelial defects were noted, but in two of these there was coexisting tear film disease. One other patient receiving acyclovir ointment had a minor degree of superficial punctate epitheliopathy. This disappeared quickly and was not considered significant. Some stinging was reported by three patients, two receiving acyclovir tablets and one receiving acyclovir ointment.

Four patients (three who had received oral acyclovir and one who had received acyclovir oint-

ment) subsequently developed disciform keratitis. One patient treated with acyclovir ointment had a recurrence of his dendritic ulcer three weeks after the initial lesion had healed.

Discussion

Locally applied acyclovir ophthalmic ointment is now accepted as a standard treatment for corneal epithelial herpetic keratitis. There is a group of patients, as mentioned above, who would benefit from an effective oral medication. This study has shown that oral acyclovir is as effective as locally applied acyclovir in the management of herpes simplex dendritic corneal ulceration.

The mean trough plasma level of acyclovir in the study patients who received oral drug (3.28 μM) is similar to values reported previously.^{16,17} These levels are considerably lower than the concentrations of drug routinely achieved by intravenous administration¹⁸ and are therefore well within tolerance limits. The mean in-vitro ID₅₀ values for herpes simplex virus type 1 range from 0.08 to 0.5 μM acyclovir.¹⁹ The mean trough acyclovir concentration in the tear fluid of patients taking the oral drug (0.6 μM) was above the upper end of this range, and all individual values fell within or above the sensitivity range of the virus.

As there were no significant systemic or local side effects, oral medication would therefore appear to provide an acceptable alternative for patients who are unable or unwilling to use local treatment for their disease. This study has shown that 400 mg of acyclovir given five times daily by mouth would be an effective alternative therapy in selected patients in the management of dendritic corneal ulceration.

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Table 2 Acyclovir concentrations in tear fluid and plasma following oral or topical administration

Oral acyclovir			Acyclovir ophthalmic ointment		
Patient number	Acyclovir concentration (μM)		Patient number	Acyclovir concentration (μM)	
	Tear fluid	Plasma		Tear fluid	Plasma
1	<0.01*	0.96	3	>5.0	<0.01
2	<0.01*	6.62	4	>11.0	<0.01
6	0.16	1.83	5	>9.0	<0.01
8	0.28	1.39	7	>3.0	<0.01
9	0.36	6.08	10	3.73	<0.01
12	1.01	2.06	11	42.7	<0.01
14	0.43	2.23	13	—	<0.01
16	1.28	4.28	17	34.3	<0.01
19	0.92	3.32	18	9.71	<0.01
22	0.22	3.03	20	>130.0	<0.01
23	1.08	6.62	21	1.87	<0.01
25	0.27	3.16	24	108.32	<0.01
27	0.25	1.78	26	42.84	<0.01
29	1.45	6.87	28	78.43	<0.01
31	1.17	8.79	30	0.34	<0.01
32	0.09	1.71	33	131.74	<0.01
35	0.26	1.49	34	15.05	0.01
36	0.12	1.45	39	524.91	<0.01
41	0.74	1.69	44	75.13	<0.01
42	0.20	2.47	48	46.27	0.01
45	0.69	4.49	49	0.80	<0.01
46	0.76	2.85	50	50.32	0.01
47	5.26*	2.03	51	428.34	<0.01
52	1.55	—	55	0.87	<0.01
54	0.17	1.50	57	2068.44	0.01
56	0.71	3.81	58	91.19	0.01
60	0.24	2.75	59	19.15	<0.01

* Values excluded from calculation of mean: low sample volumes prevented accurate assay.

age. Each patient was seen at least three times weekly or more frequently if necessary. If there were any doubts about a patient's ability to comply with the dosing regimen or if the ulcer was particularly large the patient was admitted to hospital at the beginning of treatment. Mydriatics and eye padding were used as appropriate. The diagnosis was based on the history and clinical appearance of the lesion, and at each visit a full ocular examination was carried out and the results recorded.

On a random basis patients were allocated either 3% acyclovir ophthalmic ointment and placebo tablets, or placebo ointment and acyclovir tablets (400 mg). All medication was to be taken five times daily. If the condition showed no improvement within four days, deteriorated at any time during the study, or failed to heal by 14 days the patient was withdrawn and alternative treatment was given. Healing was deemed to have taken place when there was no further staining with fluorescein, though slight irregularity or cystic change in the epithelium might still exist. All possible adverse reactions were recorded. Blood and tear fluid samples were collected from all patients approximately 48 hours after starting treatment, for measurement of acyclovir concentrations. The specimens were collected four hours after the previous dose for standardisation of all measurements at approximately the trough levels, and acyclovir concentrations were measured by radioimmunoassay conducted by the Department of Clinical Pharmacology, Wellcome Research Laboratories.

Treatment groups were compared on entry for sex, whether they had experienced a previous attack, whether there was any uveal involvement, and for ulcer size by a χ^2 test. A *t*-test was used to compare the ages of the two groups. The duration and severity of their symptoms and the extent of stromal infiltration were compared between groups by the non-parametric Mann-Whitney U test. The time to healing after starting treatment was compared between the two groups by a log rank analysis.

Results

Of the 60 patients who entered the study three receiving the oral medication failed to come for follow-up, and one was lost from the local therapy group. Statistical analyses showed that there were no significant differences between the treatment groups at entry in any variable (Table 1) except that the group receiving oral acyclovir had a significantly longer duration of symptoms ($p < 0.05$). The duration of symptoms prior to therapy was included as a covariate in a regression analysis for time to healing after starting treatment. There was no relationship

Table 1 Summary of patient characteristics at presentation

	Oral acyclovir	Acyclovir ophthalmic ointment
Sex: male	21	24
female	6	5
Age (years), mean	44.7	50.0
Previous attack, percentage	29.6	51.7
Duration of symptoms (days), mean	7.6	4.6*
Severity of symptoms (score), mean	2.3	2.3
Stromal infiltration (score), mean	0.7	0.8
Uveitis, percentage	25.9	34.5
Ulcer size: small	8	9
large	11	9
multiple	8	11

* $p < 0.05$.

between symptom duration and healing time, and the difference between the two groups at entry was considered unlikely to bias the results.

There was no significant difference between the treatment groups in the number of patients healed by 14 days. Healing was achieved in 24 (88.9%) of the 27 oral acyclovir recipients and in 28 (96.6%) of the 29 patients treated with acyclovir ophthalmic ointment. The median time to healing (five days) was identical for both groups (Fig. 1).

Trough levels of acyclovir approximately four hours after the previous dose were determined. For patients receiving oral acyclovir samples of tear fluid and plasma were obtained an average of four hours after the dose on the second day of therapy and after an average of 9.6 previous doses. Samples of tear fluid from 24 patients and plasma from 26 patients were included in the calculation of mean values (Table 2). The mean trough concentrations of acyclovir were $0.6 \mu\text{M}$ (range 0.09 to $1.55 \mu\text{M}$) in the tear fluid and $3.28 \mu\text{M}$ (range 0.96 to $8.79 \mu\text{M}$) in the plasma.

For patients receiving acyclovir ophthalmic oint-

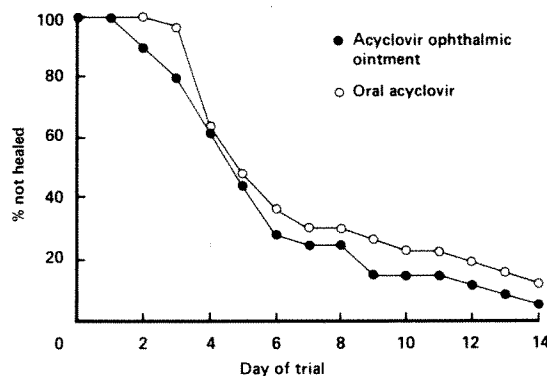


Fig. 1 Cumulative frequency distribution of time taken to heal.

Oral acyclovir (Zovirax) in herpes simplex dendritic corneal ulceration

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SUMMARY Sixty patients with simple dendritic corneal ulceration were randomly assigned to double blind treatment with either acyclovir tablets (400 mg) or acyclovir ophthalmic ointment administered five times daily. There was no significant difference in the proportions of patients healed in either treatment group (88.9% on oral acyclovir and 96.6% on acyclovir ointment). The median healing time was five days in both groups. No systemic or significant local side effects were noted in either treatment group. Trough levels of acyclovir in the tear fluid of those who received the oral preparation were within or above the range of mean in-vitro ID₅₀ levels for herpes simplex virus type 1. We conclude that oral administration of acyclovir (400 mg, five times daily) may be an effective alternative to topical therapy in selected patients.

Acyclovir is a highly effective antitherpes agent and has a selective action against herpes virus infected cells.^{1,2} Jones *et al.* in 1979³ showed that acyclovir was effective clinically in the control of herpes simplex eye infections, and since then it has been shown to be at least as effective as,^{4,5} or more effective than,^{2,11} idoxuridine and adenine arabinoside, and broadly equivalent to trifluorothymidine¹² in the management of dendritic corneal ulceration. There have been no significant side effects associated with its use, and it has been shown to be an acceptable alternative to any of the other antiviral agents.¹³

There is no doubt that the local antivirals available are effective in the management of herpes simplex dendritic corneal ulceration. Nevertheless there are patients who find it extremely difficult to use local treatment, either because they are unwilling to instill medication into their eye, or because they are either psychologically or physically unable to do so. Patients who have Parkinson's disease or rheumatoid arthritis, those who are elderly and unable to perform simple chores, and those whose occupation may prevent them from instilling ointment into their eye during the working day would therefore benefit from a safe, effective oral medication which would be more acceptable and easier for them to take. In addition the use of a systemic antiviral may produce

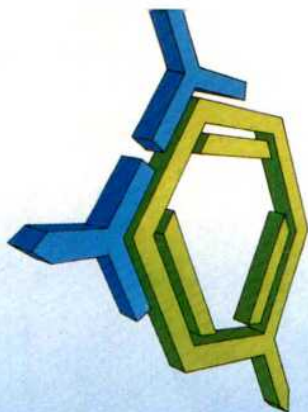
an effect deeper in the eye and might be useful in more complicated forms of herpes simplex ocular disease, such as stromal keratitis or uveitis. Systemic acyclovir has been extensively used in the management of herpes simplex mucocutaneous disease,¹⁴ with remarkably few side effects. It has been shown that in patients receiving oral doses of 400 mg acyclovir five times daily the levels of drug in the aqueous humour were in excess of the normal in vitro ID₅₀ range for herpes simplex virus type 1.¹⁵

A pilot study carried out at the Royal Victoria Eye and Ear Hospital, Dublin, in which eight patients were treated with oral acyclovir for simple dendritic ulceration resulted in the condition healing in all of them. Because of this apparently favourable response a double blind controlled study was set up to compare the efficacy of oral and local acyclovir in the management of simple dendritic corneal ulceration. This paper reports the results of this study.

Material and methods

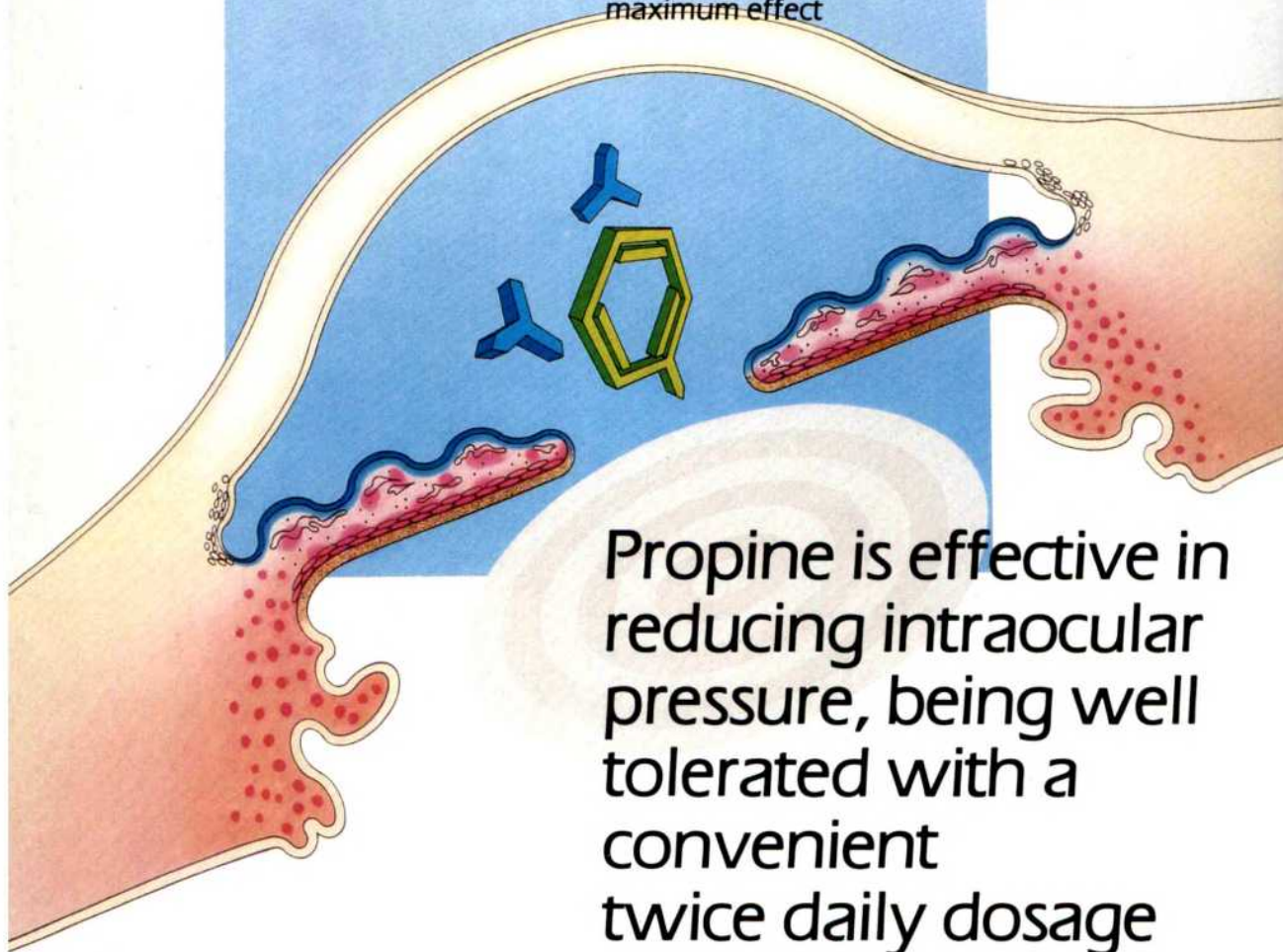
Sixty patients with simple dendritic corneal ulceration were included in this study, having given their informed consent. Excluded were those who had been treated with antivirals within the previous six months, those who had used topical steroids at any time, and those who had any other associated ocular disease. Also excluded were unocular patients, children under 14 years, and women of child bearing

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Table 3 Levels of anti-VZV and anti-HSV1 IgG in 27 patients with HZO

Patient	Onset (days)	Anti-VZV	Anti-HSV1*
1	12	2048	32
2	90	128	0†
3	5	2048	16
4	5	512	0
5	—	2048	32
6	14	512	0
7	42	1024	64
8	21	512	0
9	—	64	16
10	—	512	16
11	6 yr	32	16
12	5	2048	32
13	14	1024	128
14	12	512	64
15	8	2048	32
16	12	1024	64
17	15	1024	0
18	10	2048	0
19	28	512	128
20	6	128	256
21	11	512	128
22	50	1024	64
23	7	512	16
24	1	16	0
25	28	1024	256
26	12	1024	128
27	10	2048	16

* Determined by using an indirect microimmunofluorescence test.⁵

† 0=<16.

Cradock-Watson *et al.*⁴ found IF to be more sensitive than the complement fixation test in detecting VZV antibodies, but even in their study the range of these antibodies in HSV patients was relatively low (titres 8 to 64).

Anti-VZV IgM was found in only six of the 134 patients with HZO. Various authors have suggested that the presence of IgM is uncommon in zoster, which is usually considered a secondary VZV infection.^{9,10} However, others have found IgM in acute varicella or zoster by the IgM capture radioimmunoassay (RIA) test,¹¹ IF,⁴ and RIA.¹² The differences in IgM detection

between this study and that of Cradock-Watson *et al.*, who found IgM in 75% of 55 patients with herpes zoster, is difficult to explain. However, the difference may be related to the differences in methods and patient selection.

The authors are grateful to the staff of the Zoster Clinic and the Keratoconjunctivitis Clinic for the collection of specimens. The study was supported by a grant from the DHSS administered by Moorfields Eye Hospital.

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results show that 107 of the 134 (80%) of the sera from patients with HZO had a titre of ≥ 256 . In comparison, only two out of a total of 216 patients (1%) with ocular problems other than those of HZO had a titre of ≥ 256 (Table 2).

Level of anti-VZV IgM in patients with HZO. IgM at a level of 1 in 8 was found in 6 of the 134 sera from patients with HZO.

Cross reactivity with HSV 1. Sera of 27 patients with HZO were tested against HSV-1 antigen in addition to the VZV antigen. Twenty-one had an anti-HSV1 IgG titre of 64 or less, four had a titre of 128, and the remaining two had a titre of 256. In all but two samples anti-VZV IgG titre was at least fourfold greater than the anti-HSV1 titre.

Anti VZV IgG titres and skin lesions. The results are presented in Fig. 2. Anti-VZV IgG titres increased within about four to six days of onset of skin lesions of HZO and appeared to fall to baseline levels after the second month.

Discussion

In this study a simple, practical, and reproducible serological test has been developed for the diagnosis of HZO using a single serum sample. It has been possible to make a provisional diagnosis of HZO with a high degree of confidence.

Previous studies evaluating immunofluorescence (IF) serological tests for the detection of antibody against VZV have used human diploid cells with a

limited life span for the preparation of antigen.¹⁷ In this study we used HeLa cells, which have the advantage of being a continuous cell line. HeLa are known to be satisfactory for maintenance of VZV in serial passage and for the preparation of complement fixing antigen.⁸

The use of fixed monolayers as antigen makes the morphology of VZV plaques well preserved: specific fluorescence was confined to the plaques or foci of VZV-infected cells which result from the cell to cell spread and was not seen in the surrounding uninfected HeLa cells (Fig. 1). This makes the end point easier to read and would explain the good reproducibility of the test (Table 1). Previous workers have used infected cell monolayers as antigen, but the methods of preparation have been cumbersome.¹⁷ The fixed antigen slides stored at -20°C could be used for at least three months and thus are practical for routine use. The test is economical, since the Belco chambers make it possible to have 10 infected monolayers on the same slide.

The test showed a high degree of sensitivity and specificity in the differential diagnosis of HZO from other ocular viral infections. The results show that 80% of the 134 sera from patients with a clinical diagnosis of HZO had anti-VZV IgG titre of ≥ 256 . Such titres were found in only 2 of 216 sera from patients with a clinical diagnosis of ocular 'viral' infections. In 27 (20%) of the HZO patients lower titres (<256) were found. Two-thirds of these were probably due to early collection of sera because they were taken within one week of onset of rash. In addition a review of clinical diagnosis in 17 cases showed that one had a probable HSV infection and in two the diagnosis of zoster was not confirmed clinically.

Anti-VZV IgG was present in all the sera of patients with HZO studied here. The titres increased rapidly, usually within a week, peaked at 10 to 15 days, and appeared to fall after the second month (Fig. 2). Thus the test has an obvious advantage in cases of chronic infection or late acute cases. The number of observations after two months was small for any valid conclusion to be drawn beyond this period.

The problem of cross reactivity between VZV and HSV infections has been noted previously.⁹ In this study anti-VZV IgG was detected in all 21 patients with HSV ocular infections but only in low titres ranging from 16 to 64 (Table 2). Anti-HSV1 IgG was also detectable in HZO patients, but, again, the majority had titres in the range of up to 64 (Table 3). This suggests a degree of cross reactivity between these viruses. However, the degree of cross reaction detected was not sufficient to interfere with the interpretation of the result for the diagnosis of HZO.

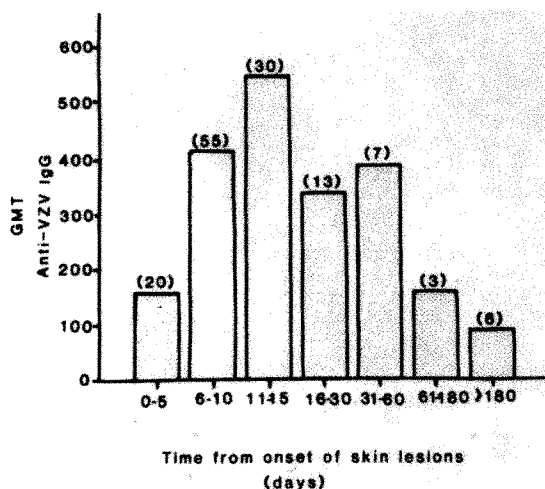


Fig. 2 Correlation between levels of anti-VZV IgG titres and time from onset of skin lesions in HZO patients. Each bar represents geometric mean anti-VZV IgG titres in HZO patients at various times after onset of skin lesions. Figures in parentheses indicate numbers of observations for each time interval.

Postural behaviour of intraocular pressure in diabetics

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SUMMARY The response to posture of intraocular pressure (IOP) was studied in 58 normal and 60 diabetic eyes. A significant postural rise of IOP was found in the diabetic patients. The clinical relevance of the abnormality in pressure regulation in diabetics is discussed. Its implications for other closely associated disorders are emphasised.

Diabetes mellitus is now becoming one of the leading causes of blindness, especially in elderly people. Ocular complications of diabetes tend to increase in frequency with the duration of diabetes but bear little relation to the severity of the disease. The incidence of primary open-angle glaucoma is said to be higher in diabetic than in non-diabetic people, suggesting a close relationship between diabetes and this kind of glaucoma.¹ An abnormal postural response of the intraocular pressure (IOP) bilaterally has been reported in cases of unilateral central or tributary retinal vein occlusion.² An abnormality of pressure regulation in these patients has been suggested.³ Such retinal vascular occlusions are more common than usual in diabetes mellitus⁴ and open-angle glaucoma.⁵ It was therefore decided to investigate the postural response of the IOP in diabetic patients because clinical data on this aspect of diabetes are surprisingly lacking.

Materials and methods

Thirty normal persons above the age of 40 years were

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carefully selected from the Ophthalmic Clinic of University Kebangsaan, Malaysia. Thirty diabetic patients above the age of 40 years were also selected from the medical units of University Kebangsaan, Malaysia, and the General Hospital, Kuala Lumpur. There was no evidence of any inflammatory eye disease in the normal or diabetic individuals. Patients with significant respiratory or cardiovascular disease or with any family history of glaucoma were excluded. None of the normal subjects was receiving any systemic or local medication.

Perkins' hand-held applanation tonometer was used to measure the intraocular pressure (IOP) throughout this study. The subject was asked to sit in a chair. Both eyes were anaesthetised with 0.4% oxybuprocaine eye drops and were lightly stained with fluorescein dye. The IOP was measured first in the sitting position in each eye separately. The subject was then asked to lie down on the examination table. No pillows were given to support the head. After about five minutes the IOP was measured in the supine position in each eye. All measurements were done by the same observer (MS). An average of three measurements was taken as the final reading. Cases showing more than 2 mmHg difference in IOP rise between the two eyes were not considered.

Table 1 Age and sex distribution

Age group in years	Control		Diabetic		Total	
	Male	Female	Male	Female	Male	Female
41-50	1	2	2	1	3	3
51-60	4	7	6	8	10	15
61-70	6	4	7	5	13	9
71-80	4	2	0	1	4	3
Total	15	15	15	15	30	30

docility at times in some animals, with consequent difficulty in achieving satisfactory readings. None of the starting rabbits was subsequently rejected. A better plan would be to screen a larger cohort of animals some of which could be excluded before randomisation during a longer run-in period of a few weeks; the study would then start with a valid base line control week just before the experimental weeks.

We consider that the lack of significant effect in weeks II and III may be attributable partly to high variance as much as to a possibly slow build up of effectivity of the drug (such as probably applies in steroid-induced glaucoma). Our previous study suggested a delay in effectivity.^{9,10}

Any small difference between the response of the six slightly younger and lighter albino rabbits and the other six slightly older and heavier black and white rabbits would not allow valid conclusions about a difference in susceptibility, mainly because of paucity of numbers.

We take this opportunity to summarise our experience from four series of randomised rabbit experiments (see Table 2). For each posttreatment two weeks Table 2 shows the pooled 95% confidence interval for the mean difference (vehicle minus RU486) per reading of ocular tension (this assumes that the effect of the drug is the same in each trial). There is some suggestion in Table 2 of a lesser effect in the first treatment two weeks compared with the second, third, and fourth two weeks posttreatment.

Although the fall in pressure produced by RU486, a peripheral corticosteroid blocking drug, is small in rabbits, we expect a clinically useful effect in patients with or predisposed to open-angle glaucoma. Clinical trials are planned. The antiprogesterone properties of RU486 have already attracted clinical use in various situations.¹¹ In the longer term two different sets of drugs will probably evolve, one with *selective* corticosteroid blocking properties and another with *selective* progesterone blocking attributes.

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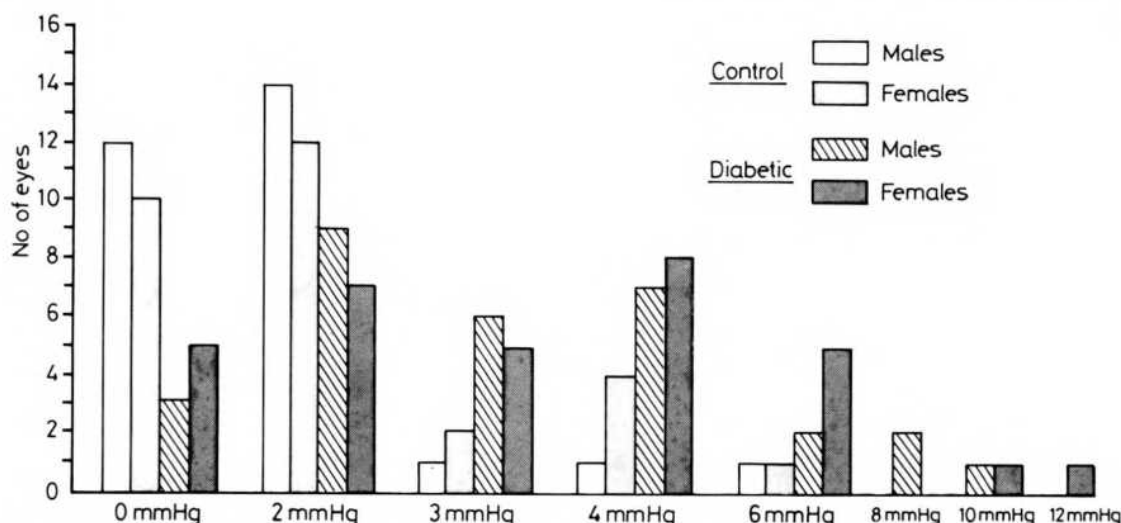


Fig. 1 Histogram of pressure differential between patients sitting and lying down. $P_o = LIOP - SIOP$ mmHg.

diabetic subjects had any significant hypertension and none was on antihypertensive medication.

Retinal vascular occlusions are said to be unusually common in diabetic as well as in chronic simple glaucoma.¹ The risk of suffering such retinal vascular accidents increases in the presence of systemic hypertension. It has been suggested that in these cases the eyes may share a common defect which predisposes them to develop these abnormalities.⁶ No clinical test is entirely suitable for identifying those diabetic eyes which are at risk of developing vascular accidents and open-angle glaucoma. The abnormal postural response of the IOP may become a useful test for identifying such patients early.⁶

Reference to Table 3 shows that, while the mean rise of IOP in diabetic patients as a group may be higher than that of normal control subjects, all diabetic patients do not behave in a similar way. In 38.3% of our diabetic eyes the IOP rose by only 2 mmHg (Fig. 1). Eleven diabetic eyes in this study showed a postural rise of IOP of 5–12 mmHg. Such a swing in a small number of diabetic eyes is rather striking. The exact mechanism of this anomalous behaviour is not understood. A similar higher postural response has been reported in ocular hypertensives.⁷ These authors attributed it to the presence of more risk factors of chronic simple glaucoma in these patients, notably a family history of glaucoma. We have tried to exclude subjects with such a history. However, our subjective screening might have left some individuals with a genetic risk in the study.

In addition, local adrenergic receptors are said to be important for maintaining a stable IOP despite changes of posture.⁸ Inadequacy of this local regulatory mechanism might account for the pathogenesis

of this abnormal response of the IOP, especially in diabetic patients, who are apt to develop autonomic neuropathy.⁹ In a few of our cases some degree of hypertensive asymmetry between the two eyes was observed (2 mmHg). A considerable postural rise of IOP in one eye alone has already been reported in cases of ocular hypertension⁷ and unilateral chronic simple glaucoma.¹⁰ It seems to suggest there is an abnormality of pressure regulation locally within the eye in such patients.

In the present study no attempt was made to correlate the postural change of IOP with the type of diabetic retinopathy. Such a study would be useful to establish whether an abnormally high postural rise of IOP can protect the eye against the development of serious proliferative retinopathy. It is well known that a raised intraocular pressure is seen more commonly in diabetics with no proliferative changes than in non-diabetic persons or diabetic patients with proliferative retinopathy.¹ The optic nerve head is said to be more vulnerable to the IOP in diabetics.¹ As most of our diabetic patients are old, they may spend a considerable time lying supine while sleeping or otherwise, and they may thus possibly suffer optic nerve damage from an abnormality of pressure regulation. This may be relevant to the development of acute anterior ischaemic optic neuropathy in elderly people.¹¹ But the disorder remains poorly understood, and the prognosis for vision generally is poor. Evaluation of the postural response of the IOP in cases of acute optic nerve ischaemia should receive serious consideration. A significant postural change of IOP has been recently reported in patients with low-tension glaucoma.¹² It has been suggested that damage to the optic nerve in these cases might be

Results

A total of 60 diabetic and 58 control eyes were examined. The results are shown in Tables 1–3 and Fig. 1.

Both groups were closely matched for age and sex. Most of the subjects were in the age range of 51–70 years.

The mean IOP readings in each group are shown in Table 2. The average sitting intraocular pressure (SIOP) of 14.14 (SD 3.56) mmHg was found in normal Malaysian eyes. The mean SIOP in the diabetic Malaysian eyes was noted to be 15.64 (SD 3.24) mmHg. There was no significant difference in the two sexes in either group. An average rise of 1.82 (SD 0.50) mmHg in IOP on assuming the supine position was observed in normal, healthy individuals. The comparable figure of 3.58 (SD 0.51) mmHg was observed in the diabetic patients. A difference of 1.76 mmHg between the mean postural rise of IOP in the two groups was noted, which was statistically significant ($p < 0.01$).

An increase of 5 mmHg or more in IOP with postural change was used to separate a group of 11 (18.3%) diabetic eyes which registered a rise of more than 4 mmHg in IOP on changing from the erect to the supine position (average 8.84 mmHg). The remaining 49 (81.7%) diabetic eyes showed a rise of IOP of 0–4 mmHg (average 3.49 mmHg). The IOP elevation in 56 (96.6%) control eyes also varied between 0 and 4 mmHg, with an average of 1.82

mmHg. Only two (3.4%) normal eyes showed a rise of 6 mmHg. There was no significant correlation between the abnormal postural rise of IOP and duration of diabetes. However, a greater rise of IOP was noted in comparatively elderly diabetic patients, though it was not statistically significant.

From Fig. 1 it can be seen that 82.4% (48 eyes) of the control eyes showed a rise of IOP up to 2 mmHg. A similar rise of IOP in the diabetic group was seen only in 38.4% (23 eyes). The highest IOP rise of 12 mmHg was observed in one eye of a 72-year-old diabetic woman.

Discussion

Diabetes mellitus, primary wide open-angle glaucoma, and retinal vascular occlusions are clinically closely linked.^{1,2} Both diabetes and open-angle glaucoma can be exacerbated by the administration of corticosteroids.¹ An abnormally high rise of IOP can be produced by topical steroids in both groups of patients. The effects of diabetes on IOP have been studied by many workers.¹ Jain and Luthra⁴ postulated that changes in blood glucose levels may affect the IOP, and that perhaps the pattern of intraocular tension, including the variability of its responsiveness to different stimuli, may be determined genetically and influence the retinopathy thereby. A moderate rise of IOP seems to protect against the development of diabetic retinopathy with haemorrhages, as observed in cases of glaucoma and diabetes.¹ However, both diseases are thought to be interrelated genetically, as suggested by their steroid responsiveness.³ Hyperglycaemia together with a decreased pH lowers the IOP by increased serum colloid osmotic pressure.

A significant postural rise of IOP (3.58 mmHg) was seen in our diabetic patients. Williams *et al.*⁶ also found a postural rise of 4.9 mmHg in their small series of 14 diabetics. It seems that the level of IOP is not adequately controlled with change of body position in diabetic people. This abnormality is said not to be determined by coexisting systemic hypertension.⁶ Our study supports this observation, as none of our

Table 2 Average IOP measurements (mmHg) in two groups (SD in parentheses)

	Sitting IOP	Lying IOP	IOP change
<i>Control</i>			
Male (29 eyes)	14.68 (±3.32)	16.48 (±3.69)	1.79 (±0.54)
Female (29 eyes)	13.65 (±3.8)	15.00 (±4.37)	1.85 (±0.46)
Mean (58 eyes)	14.14 (±3.56)	15.96 (±4.00)	1.82 (±0.50)
<i>Diabetic</i>			
Male (30 eyes)	16.11 (±3.43)	20.02 (±3.51)	3.91 (±0.53)
Female (30 eyes)	15.17 (±3.10)	18.42 (±3.32)	3.25 (±0.49)
Mean (60 eyes)	15.64 (±3.24)	19.22 (±3.31)	3.58 (±0.51)

Table 3 Comparison of age, sex, IOP measurements, and duration of diabetes in diabetic and control subjects

	11 Diabetic eyes, IOP rise more than 4 mmHg	49 Diabetic eyes, IOP rise 0–4 mmHg	56 Control eyes, IOP rise 0–4 mmHg
Average age in years	61.5	59	56.6
Male:female	5:6	25:24	7:7
Average SIOP mmHg	15.59	15.49	14.14
Average LIOP mmHg	24.43	18.98	15.96
Average IOP rise mmHg	8.84	3.49	1.82
Average duration of diabetes in years	11.7	12.34	

SIOP=sitting intraocular pressure LIOP=lying intraocular pressure

Eye injuries in Northern Ireland two years after seat belt legislation

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SUMMARY Two hundred and forty-six patients with ocular perforation were treated at the Royal Victoria Hospital, Belfast, between 1 February 1981 and 31 January 1985. Road traffic accidents were responsible for 63 injuries, all of which affected front seat occupants, and 45 occurred before implementation of the seat belt law on 1 February 1983. Following legislation there was a 60% reduction in ocular injuries, which confirms the protective effect on front seat occupants of wearing a seat belt.

Road traffic accidents are a common cause of perforating eye injury with resulting visual loss and cosmetic disability. Johnston¹ strongly recommended the compulsory use of seat belts to protect car occupants from injury, and evidence from other countries² shows a significant decrease in eye injuries after introduction of seat belt legislation.

The compulsory use of seat belts by front seat occupants of cars was introduced to Great Britain and Northern Ireland on 1 February 1983, and Rutherford *et al.* reported a significant reduction in fatalities and injuries from car accidents during the first year after legislation.

We set up a retrospective study which examined the pattern of penetrating eye injuries in Northern Ireland during the two years immediately before and after seat belt wearing became compulsory.

Materials and methods

The Department of Ophthalmology at the Royal Victoria Hospital, Belfast, is the regional ophthalmic centre for a population of about 1.25 million. We examined the hospital records of all cases of penetrating eye injuries which were treated at the Royal Victoria Hospital from 1 February 1981 to 31 January 1985. Where injury resulted from a road traffic accident, details of the injury, the patient's age and sex, seat belt compliance, position in the vehicle, and visual recovery were recorded.

Results

Two hundred and forty-six patients with ocular perforation were treated at the Royal Victoria Hospital between 1 February 1981 and 31 January 1985 (Table 1). A total of 63 injuries were caused by car accidents during the survey, and, of these, 45 cases occurred before and 18 after seat belt legislation, which is a fall of 60% ($p < 0.001$, $\chi^2 11.57$, $df=1$).

Eight patients (Table 2) sustained injury while wearing a seat belt, and of this group one had a defective belt and another described injury by flying glass when his vehicle was stationary.

Table 1 *Distribution of eye injury by cause and year of injury*

Cause	1981-3		1983-5	
	No	%	No	%
Road traffic accident	45	33.6	18	16
Others	89	66.4	94	84
Total	134	100	112	100

Table 2 *Seat belt status of injured patients*

	1981-3		1983-5	
	No	%	No	%
Seat belt	1	2.2	7	38.8
No seat belt	44	97.8	11	61.2
Total	45	100	18	100

occurring when the patient is actually asleep in the supine position.* The postural response of the IOP should become an essential part of the overall assessment of diabetic effects on the eye.

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Of those injured before and after legislation the expected level of visual recovery is largely unchanged. Indeed, in the prelegislation period 57% of our patients regained visual acuity of 6/12 or better compared with 42% postlegislation. These figures compare with those of Blake⁹ and Canavan *et al.*,⁴ who both reported that 44% of their patients regained 6/12 or better. There was a dramatic decline in the enucleation rate before and after legislation. During 1981–3 eight injured eyes (16%) were excised and in 1983–5 one enucleation (5%) was necessary. This compares favourably with enucleation rates of 22.9% by Blake *et al.*⁹ and 20.2% by Canavan *et al.*⁴ We observed a decline in bilateral ocular perforations during the postlegislation period, which probably reflects the direct effect of legislation in reducing the total number of eye injuries and the protective effect of seat belt use against windscreen impact.

The seat belt legislation introduction to Northern Ireland on 1 February 1983 has effected a remarkable decline in the number of serious eye injuries caused by road traffic accidents. Injuries continue to occur which we believe are due to the non-use of belts, faulty belts, and injury caused by flying glass from toughened windscreens. These injuries may be

further reduced by compulsory fitting of laminated windscreens in all newly registered motor vehicles and rigorous enforcement of the seat belt legislation.

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All 63 patients were front seat occupants (Table 3), with no significant difference in the number of front seat passengers and drivers injured. There were no injuries to back seat passengers during the study.

66% of injuries affected patients aged 17-29 years (Table 4), and this age range showed a 73% reduction in ocular perforations sustained after legislation.

Table 5 shows that a greater proportion of patients retained vision of 6/6 in the injured eye in the pre-seat belt period. During the prelegislation period a greater proportion of patients were rendered totally blind in the injured eye by the accident, and the enucleation rate was greater. A total of six bilateral perforations were treated during the survey, and of

these only one occurred after the legislation. Males were more susceptible than were females to injury (Table 6).

Discussion

Road traffic accidents are a major cause of visual loss in the young adult population, and Canavan *et al.*⁴ found that they caused 30.2% of perforating eye injuries in Northern Ireland from 1967 to 1976. The ocular injury caused by a road traffic accident is usually associated with multiple facial lacerations and may be bilateral. The mechanism of injury comprises impact of the victim's head against a shattered windscreen and perforation caused by flying glass.

Seat belt wearing by front seat occupants of vehicles became compulsory in Northern Ireland on 1 February 1983, and compliance was estimated at 92% during the first year of legislation compared with 25% during 1982.³ The Royal Victoria Hospital is responsible for the treatment of almost all perforating eye injuries which occur in Northern Ireland. The records of all these injuries were examined during the two years before and after introduction of seat belt legislation. Our survey shows a 60% reduction in perforating eye injuries following legislation, which corresponds with observations in Wessex, England, by Hall *et al.*,⁵ who reported a 73% reduction in the immediate postlegislation year, and Vernon and Yorston,⁶ who found a 58% reduction during comparable six-month periods before and after compulsory seat belt use. A multicentre report by Rutherford *et al.*³ showed a decrease by 83.3% of perforating wounds to the eye in the year after legislation. The significant drop in ocular perforations which followed seat belt legislation in Northern Ireland is not explained by a reduction in road traffic accidents, which increased from 5249 in 1981 to 5978 in 1984.⁷

It is clear that the risk of serious ocular injury by windscreen impact is greatly reduced by seat belt use. However, seat belts do not protect against injury by flying glass. Blake *et al.*⁸ emphasised the danger of flying windscreen glass as a cause of ocular perforation, and reported⁹ that in spite of compulsory seat belt legislation eye injuries in the Republic of Ireland continued to occur at a high rate of 99 injuries in 5182 accidents during 1981. We found an average of nine eye injuries in 5701 accidents following seat belt legislation, and, of these, 39% were injured while wearing seat belts. Our observations support the view of MacKay¹⁰ that eye injuries to car occupants could be further reduced if laminated instead of toughened windscreens were used in addition to seat belt use.

Table 3 Position of injured person in vehicle

	1981-3		1983-5	
	No.	%	No.	%
Driver	23	51	10	55.5
Front seat passenger	22	49	8	44.5
Total	45	100	18	100

Table 4 Distribution of injured patients according to age

Age when injured (years)	1981-3		1983-5	
	No.	%	No.	%
0-16	2	4.4	3	16.6
17-29	33	73.3	9	50.0
30+	10	22.3	6	33.4
Total	45	100	18	100

Table 5 Distribution of eye injuries by final visual acuity

Acuity	1981-3		1983-5	
	No.	%	No.	%
6/6	15	30.6%	4	21.0%
6/9-6/12	13	26.5%	4	21.0%
6/18-6/36	5	10.2%	5	26.3%
6/60 or worse	4	8.1%	4	21.0%
No perception of light	12	24.5%	2	10.5%
Total	49*	100.0%	19	100.0%
Enucleation	8	16.0%	1	5.0%

*One patient lost to follow-up.

Table 6 Distribution of injured patients by sex

	1981-3		1983-5	
	No.	%	No.	%
Male	30	66.6	13	72.2
Female	15	33.4	5	27.8
Total	45	100	18	100

who were born in UCH and 91 who were transferred from other centres within one week of birth. The eyes of 177 of the 199 surviving infants were examined, and these 177 infants are the subject of this report. Of the remainder, 22 infants failed to keep appointments, five moved out of the country, and two moved to another city shortly after discharge from hospital.

Clinical management. Methods of management of the infants, many of whom were seriously ill, were in general as described previously.¹⁵ Particular attention was paid to the monitoring of blood gases by the use of continuous intra-arterial¹⁶ or transcutaneous techniques.¹⁷

Ultrasound. The brains of all the infants were scanned with ultrasound, daily for the first week of life and thereafter once or twice weekly until the infants were discharged or died, as described elsewhere.¹⁸

Ophthalmological examinations. Where possible, a fundus examination was performed in the neonatal unit about two weeks after oxygen therapy ceased. All infants were then examined shortly after discharge from hospital in a special follow-up clinic as part of an ongoing study of outcome in very preterm infants. At this examination the ability to fixate on a large bright object was first assessed and the pupil responses were noted. Disorders of ocular motility were characterised, and where possible the presence or absence of amblyopia was assessed by the Catford drum.¹⁹ Mydriasis and cycloplegia were then produced with 0.5% cyclopentolate drops. Children with heavily pigmented irides required additional 2.5% phenylephrine drops to achieve adequate pupil dilatation. The refraction was determined objectively by retinoscopy prior to fundus examination by indirect ophthalmoscopy. Any degree of myopia was regarded as abnormal. Hypermetropia and astigmatism of small degree are physiological and were not considered abnormal unless greater than 1.0 or 0.5 dioptre respectively. Fundus examination by indirect ophthalmoscopy confirmed the presence or absence of ROP. When diagnosed, ROP was classified according to five stages of development as described by Keith.^{20, 21}

DVM was diagnosed when the fixation reflex could not be elicited in the alert, wakeful child, when both eyes were structurally normal, and when there was no evidence of roving eye movements or abnormality of the pupil responses to light.²²

Follow up. Perinatal details were recorded prospectively, coded, and stored for later computer analysis. At follow-up in addition to ophthalmological examinations the investigations included neurological, otological, audiological, and developmental assessments in the first 18 months of life. As the children grew older, language, cognitive

functioning, and motor skills were assessed. Details of the methods employed have been described previously.¹⁸

Results

The eyes of 84 of the 177 infants were first examined in the Neonatal Unit. They were examined again together with the eyes of the remaining 93 infants in the follow-up clinic until a maximum age ranging from 3 to 40 months (median 18 months), after correction for preterm birth. One of the 22 infants who was not examined died aged 24 months. This infant was profoundly abnormal, with cerebral palsy and overall developmental delay, including absent visual responses. The remaining 21 infants were seen in our own or other follow-up clinics as they grew older and were considered on clinical grounds to have satisfactory vision.

Fourteen (8%) of the 177 infants whose eyes were examined had fundus signs of ROP, including 9 (11%) of the 84 infants first examined in the Neonatal Unit. The signs were bilateral in all 14, though not necessarily symmetrical. In 11 infants ROP did not progress beyond stage I-II. None of these 11 received active treatment and none developed cicatricial retinopathy. The condition resolved spontaneously in four with no ocular sequelae. Six of the other seven infants developed myopia, associated with a convergent squint in one. The seventh child had a convergent squint only. Three infants developed stage III ROP. One infant, with stage IIIB disease, had cryotherapy abroad with a good visual result and no evidence of progressive cicatricial change. The other two infants with stage III disease were not treated. Both developed low myopia, associated in one of them with a divergent squint and delayed visual maturation. Neither infant developed cicatricial retinopathy, and both had satisfactory vision after correction of the refractive error. Details of all 14 affected infants are shown in Table 1.

Refractive error. Almost all the 84 infants examined before discharge from hospital were myopic (-0.50 DS to -7.0 DS) during the neonatal period. By contrast just 17 (6%) of the total of 177 infants in the study had errors of refraction which persisted beyond this period, including eight with ROP.

Amblyopia and disorders of ocular motility. Twelve (7%) infants had amblyopia or abnormal ocular movements. In all instances the defect was first detected in the outpatient clinic more than three months after birth.

Delayed visual maturation. Nine (5%) infants showed no visual awareness nor made following responses to a bright light at the first outpatient examination, aged 1 to 12 weeks (after correction for

Ocular sequelae of preterm birth and their relation to ultrasound evidence of cerebral damage

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SUMMARY The eyes of 177 very preterm (<33 weeks' gestation) infants, born between 1979 and 1982 and admitted to a neonatal intensive care unit, were examined as part of an ongoing follow-up study of neurodevelopmental outcome. Ocular pathology was diagnosed in 37 (21%) of the 177 infants: 14 (8%) had retinopathy of prematurity (ROP)—progressive in three—and nine (5%) infants had delayed visual maturation (DVM). The ocular pathology was permanent in 26 (15%) of the 177 infants. Refractive errors were the commonest problem and accounted for permanent sequelae in eight of the 14 infants with ROP and two of the nine with DVM. The presence or absence of ROP was related to a wide range of prospectively coded perinatal variables and to the results of routine neonatal ultrasound brain scans and neurodevelopmental follow-up assessments made in the first 18 months of life. As in previous studies, infants with ROP were of shorter gestation, lower birth weight, and required oxygen therapy for longer than unaffected infants, but the condition was only weakly associated with other indices of respiratory illness. In contrast, ROP was strongly associated with evidence of brain damage, often consistent with hypoxic ischaemic injury. We conclude that an underlying lesion in ROP may be hypoxic ischaemic damage to the retinal circulation.

Defective vision has been reported frequently as a cause of permanent handicap in surviving preterm infants.¹ The impairment described has usually been due to retrolental fibroplasia, more recently termed retinopathy of prematurity (ROP),² and this condition remains the only visual disorder almost exclusively related to the perinatal period.³ Refractive error,⁴ strabismus,^{5,6} and more recently amblyopia⁷ and delayed visual maturation (DVM)⁸ have also been reported in association with preterm birth, though these conditions may be encountered in infants born after a normal period of gestation.

Changing trends in the prevalence of individual visual problems have been reported.¹ For example, there was a substantial fall in the proportion of very low birth weight (VLBW <1500 g) infants who were blind because of ROP in the years following the

recognition of its association with oxygen therapy in the 1950s. But early hopes that ROP might be eliminated by careful attention to the monitoring of arterial blood gas tensions during oxygen therapy⁹ have not been fulfilled.¹⁰⁻¹² Concern has recently been expressed that, despite the introduction of improved techniques for continuous monitoring during oxygen therapy, the prevalence of ROP among very preterm infants may be rising again.^{1,10,14} The purpose of this report is to describe the visual status at follow-up of 177 very preterm infants prospectively studied over a period of 3½ years, and to explore the pathogenesis of ROP in this population of infants.

Material and methods

Infants studied. Two hundred and seventy-seven infants born before 33 weeks of gestation were admitted to the Neonatal Unit of University College Hospital (UCH), London, between January 1979 and June 1982. One hundred and ninety-nine of these infants survived the neonatal period, including 108

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Table 2 Relationship of ROP and DVM with perinatal factors, ultrasound findings, and neurodevelopmental status at follow-up at ages 12–18 months

	ROP		DVM	
	No, n=163	Yes, n=14 (n=9)*	No, n=168	Yes, n=9
Birth weight, g, median (range)	1350 (600–2500)	1089+++ (680–1740)	1337 (600–2500)	1183 (680–1735)
Gestation, weeks, median (range)	30 (24–32)	28++++ (24–32)	30 (24–32)	30 (26–32)
Boys/girls	90/73	8/6	95/73	3/6
Vaginal delivery	92	12	97	7
Caesarian section	71	2	71	2
Apgar <3, 1 min	45	5	46	4
Base deficit ≥15 mmol/l, <2 hours of age	3	2	4	1
Hyaline membrane disease	88	10	94	4
Apnoeic spells	86	12 (7)+	92	6
Mechanical ventilation	97	13 (8)+	102	8
Oxygen therapy	143	13 (9)	147	9
Duration of oxygen therapy, days, median (range)	9 (1–105)	53++++ (1–106)	13 (1–106)	22 (1–81)
Hypertensive episodes†	70	11++	74	7
Serum bilirubin ≥170 µmol/l	88	9	94	3
Periventricular haemorrhage‡	66	11 (7)++	70	7
Ventricular dilatation, hydrocephalus, atrophy‡	29	7 (4)++	32	4
Hypoxic ischaemic injury	12	5 (3)++++	15	2
Neurodevelopmental disorder‡	29	11 (6)+++++	37	5

*Number of infants with permanent sequelae

†Recorded episodes of systolic blood pressure >2 standard deviations above the mean for gestation³⁷‡See footnote to Table 1 for definitions^{1a, 1b}

+ = p < 0.05 ++ = p < 0.025 +++ = p < 0.01 ++++ = p < 0.005 +++++ = p < 0.0005

Refractive errors (17/177, 10%) were the most common problem and accounted for the persisting pathology in infants in whom ROP (8/14) or DVM (2/9) was diagnosed in the early months of life. The prevalence of permanent ocular pathology due to ROP was 5% (9/177), and three of these infants (1.6%) had progressive disease (stage III–IIIb ROP). None of the nine were blind. These values are much lower than those reported from other centres among comparable infants.^{23, 24} More than half (8/14, 57%) of the affected infants weighed <1000 g (extremely low birth weight, ELBW) and half (7/14) were born before 28 weeks of gestation. The prevalence of sequelae in these infants was 10% (3/31) and 9% (3/34) respectively, similar to that reported by Yu *et al.*²⁵ among ELBW infants. When refractive error, squint, or DVM did occur in the VLBW infants in this study, it was usually in association with ROP—an association which probably explains the high prevalence of both squint and refractive error reported among VLBW in the past.³ Surveillance began in the Neonatal Unit in only 84 (47%) of the infants in this study, specially chosen because they were of particularly low birth weight and very sick. The prevalence of ROP in these especially vulnerable infants was 11% (9/84). Although it is possible that

minor degrees of ROP might have resolved spontaneously before surveillance began in the outpatient clinic among the remaining 93 (53%) infants, we believe that this is unlikely, since the prevalence (5/93, 5%) among these infants did not differ significantly from that among the infants first examined before leaving the Neonatal Unit ($\chi^2=1.07$, $df=1$). Thus there is no evidence from this study of very preterm infants cared for in a modern neonatal intensive care unit of an increase in the prevalence of ROP or its sequelae in spite of greatly improved survival rates.²⁶

PATHOGENESIS OF ROP AND DVM

In this study, as in all previous ones,¹ ROP was significantly associated with apnoea of prematurity and treatment with mechanical ventilation. In addition the duration of oxygen therapy was significantly longer among the group of infants who had ROP than in those who did not develop the condition; and hypertensive episodes were recorded more frequently among infants who developed ROP than those who did not (Table 2). Nevertheless, although these factors occurred significantly more often or, in the case of oxygen therapy for longer, in the ROP-affected infants when considered as a group, many of

Table 1 Ophthalmological, neonatal, and neurodevelopmental diagnoses in 14 infants with ROP and nine with DVM

ROP	DVM	Refractive error	Squint	Gest (wk)	Birth weight (g)	HMD	Apnoea	MV	US	Neurodevelopmental disorder
+				24	842	+	+	+	PVH	Minor
+		+		25	845		+	+	PVH	Minor
+				25	955	+	+	+	PVH+VD*	Major
IIIb				25	990	+	+	+	PVH+VD*	Major
	+			26	910	+	+	+	PVH	
III		+		26	938	+	+	+	PVH+VD*	Major
+	+			27	680		+	+	PVH+VD	Major
+		+		27	1165	+	+	+	PVH	
+		+	+	28	968	+	+	+	Atrophy	Minor
+		+		28	1114	+	+	+	PVH	
	+			28	1278			+	PVH	Major (died)
+				29	940	+	+	+		Major
III	+	+	+	29	1020	+	+	+	PHH	Major
	+			30	1277	+		+		
+		+		30	1400	+	+	+	PHH+atrophy	Major
	+			30	1484	+	+	+	PVH+atrophy	Major (died)
	+			31	1060		+	+		
+			+	31	1651				Atrophy (on CT)	Major
	+	+	+	31	1735		+		PVH+VD* (atrophy on CT)	Major
+		+		31	1740	+		+	PVH	
	+			32	1205	+		+	PVH	

HMD=hyaline membrane disease, MV=mechanical ventilation, US=ultrasound

Neurodevelopmental disorders: major=disabling conditions including cerebral palsy, sensory neural hearing loss, and overall developmental delay; minor=abnormalities of tone and reflexes without functional disability¹⁴

PVH=periventricular haemorrhage: haemorrhage arising in the region of the germinal layer±intraventricular haemorrhage¹⁴

PHH=posthaemorrhagic hydrocephalus¹⁴

VD=ventricular dilatation of lesser degree than PHH^{14,36}

VD*=persistent ventricular dilatation

Atrophy=local or generalised loss of brain tissue.^{14,36} For detailed definition of ultrasound lesions, see Stewart *et al.*^{14,36}

CT=computerised tomography

preterm birth). Pupillary reaction to light was normal in all nine. A diagnosis of DVM was made. Details of these infants are included in Table 1. Visual responses were eventually detected among the seven surviving infants at a median age of six months (range three to nine months) after correction for preterm birth. No responses were detected in the two infants who died aged five months of corrected age.

Prevalence and pathogenesis. Thirty-seven (21%) of the 177 infants studied had ocular pathology at some stage of the investigation, including seven with multiple problems. In 11 of these 37 infants ROP or DVM alone was diagnosed, which resolved completely so that no permanent ocular sequelae could be detected. Thus only 26 (15%) of the 177 infants had permanent visual defects.

In order to explore the relationship between perinatal factors and ocular pathology the characteristics of the infants, neonatal investigations, illnesses and treatments, ultrasound findings, and neurodevelopmental status at follow-up were compared between unaffected infants and those with ROP, DVM, or refractive errors, amblyopia, and disorders of ocular

motility not associated with ROP. Infants with ROP differed significantly from unaffected infants in several respects, shown in Table 2. For example, they were of lower birth weight ($p<0.01$) and of shorter gestation ($p<0.005$). They were more likely to have apnoeic spells ($p<0.05$), hypertensive episodes ($p<0.025$), periventricular haemorrhage ($p<0.025$), ultrasound or computerised tomographic evidence suggestive of hypoxic ischaemic brain injury ($p<0.01$), to require prolonged treatment with oxygen ($p<0.0005$) or treatment with mechanical ventilation ($p<0.05$), and to have neurodevelopmental abnormalities ($p<0.0005$) as they grew older. In contrast none of these differences were found among any of the other groups when compared with their unaffected peers.

Discussion

PREVALENCE OF OCULAR PATHOLOGY

The prevalence of permanent ocular pathology diagnosed by a median age of 18 (range 3–40) months in this group of very preterm infants was 15% (26/177).

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the infants who did not develop the condition had similar illnesses and treatments; and one infant who developed ROP had neither apnoea nor was treated with oxygen or mechanical ventilation after the first 14 minutes of life when resuscitation was completed. Thus we infer—as have others when considering the results of previous studies¹—that no one factor is alone responsible for the condition but rather a combination of factors or circumstances.

More striking than the association of ROP with respiratory illness and its treatment was the association with other neurodevelopmental disorders at follow-up (11/14). Others have recently reported a similar excess of neurodevelopmental morbidity among infants with ROP.²⁷ Although it is reasonable to consider that the infants who have neurodevelopmental abnormalities at follow-up were the sickest ones who needed the most oxygen for longest, and were therefore the most liable to its toxic effects, there is an alternative interpretation.

The brains of all the infants in this study were scanned with ultrasound in the first days of life. Lesions were detected in 12 (86%) of the 14 ROP-affected infants, including eight (89%) of the nine with permanent ocular sequelae. In contrast, lesions were detected in the brains of less than half (71/163; 44%) of the 163 infants in whom ROP was not diagnosed (Table 2). The lesion in five of the 12 infants with ROP, including two of the three infants with stage III disease, was considered to be consistent with hypoxic ischaemic injury. Likewise seven of the nine infants with DVM had periventricular haemorrhage (PVH); two had additional ultrasound evidence consistent with hypoxic ischaemic brain injury, and five had neurodevelopmental disorders at follow-up. Hypoxic ischaemic lesions diagnosed with ultrasound are known to be closely associated with neurodevelopmental disorders.²⁸ Thus there is strong evidence of brain damage, often of hypoxic ischaemic origin, in the majority of the infants with ROP, including all three with stage III disease, and to a lesser extent in infants with DVM. This suggests that the same set of circumstances that cause hypoxic ischaemic damage to the immature brain may also cause ROP and possibly DVM.

Procianny *et al.*²⁹ have previously reported an association between PVH and ROP. As in our study, this association was stronger than that between ROP (all cases as well as those with sequelae) and respiratory illness or treatment with oxygen. These authors pointed out that there are good theoretical reasons for such an association. Both conditions are vascular circulatory disorders affecting immature blood vessels, and both the ocular and cerebral circulations share a common origin, the internal carotid artery. Factors which regulate cerebral blood flow act in

similar ways on the regulation of the retinal circulation,^{29,30} and several of these factors have been implicated in the aetiology of PVH, notably hypercarbia, asphyxia, and hypoxaemia.^{31,32} Bracher *et al.*³³ using a photographic technique to observe retinal vessels in newborn infants, noted in asphyxiated infants that the response of retinal arteries to extremes of circulatory oxygen tensions appeared to be abolished. Thus the vessels remained dilated in the presence of high levels of oxygen in the immediate newborn period and constricted in the presence of hypoxaemia and hypotension when the infants were a little older. These are just the circumstances hypothesised by Silverman³⁴ as prerequisites for retinal damage, on the basis of the results of animal experiments by Flower *et al.*³⁵

The present study, by combining information from prospective neonatal brain ultrasound scans and detailed neurodevelopmental assessments made throughout the first 12–18 months of life, provides evidence of an association between ROP and brain injury, often of hypoxic ischaemic origin. Our data support proposals that an underlying lesion in ROP may be hypoxic ischaemic damage to the retinal circulation.³⁶

Many colleagues helped with this study and we wish to thank them. Special thanks are due to Professor EOR Reynolds for his help and support throughout the study and with the preparation of the manuscript, and to Miss Jan Townsend, who organised our joint clinics which made this study possible.

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Fig. 2 Close-up of the left eye.

10 mmHg by the Goldmann applanation tonometer.

A percutaneous liver biopsy was performed, and this showed chronic aggressive hepatitis with cirrhosis. Special histochemical stains for copper were positive. The liver copper concentration was raised at 3.1 µg/mg (normal <1.0). The 24-hour urinary excretion of copper was 3.4 and 4.6 µmol on two consecutive days. There was a positive response to D-penicillamine, with copper excretion rising to 14 µmol per 24 hours. Apart from the serum ceruloplasmin level, which was normal at 0.22 g/l, these findings supported the diagnosis of Wilson's disease.

Unfortunately his liver further decompensated and he collapsed and died two weeks later of a pulmonary embolism. Histological study of the eye was not possible.

Discussion

The Kayser-Fleischer corneal pigment ring is said to be diagnostic of Wilson's disease (hepatolenticular degeneration).¹ It is not necessarily present in pre-symptomatic cases but is present in all cases of Wilson's disease with neurological involvement.² Corneal pigment rings have also been seen, however, in cases of primary biliary cirrhosis and chronic active liver disease not due to Wilson's disease³ and in cases of multiple myeloma.^{4,5} Corneal pigment rings should therefore not be regarded as pathognomonic of Wilson's disease in the absence of neurological symptoms.⁴

The corneal ring in Wilson's disease appears first as an arc in the corneal periphery from 10 to 2 o'clock, extending from the corneal margins centrally. This is followed by a similar inferior arc, the two then spreading round the circumference. The ring is densest peripherally, ending at Schwalbe's line, and rarely extends more than 5 mm centrally. The

variable position of Schwalbe's line is thought to be the reason for varying descriptions of Kayser-Fleischer rings as having, or not having, a clear ring of cornea peripherally.⁶ Copper is deposited in the inner part of Descemet's membrane in the form of granules which may,^{7,8} or may not,⁹ be in zones. It is this 'copper chelate' which accounts for Kayser-Fleischer ring. However, the cornea is also permeated by ionic copper. This accounts for the high concentration of copper in the cornea found by spectroanalytic study¹⁰ and for the lack of correlation between the appearance of a Kayser-Fleischer ring and the corneal copper as measured by x-ray excitation spectrometry.¹¹

Deposition of granular copper material has been attributed to cellular activity, the granule production being related to formation of basement membrane by endothelial cells.¹²

Kayser-Fleischer rings disappear in the reverse order to their formation on treatment with D-penicillamine¹³ and after liver transplantation.¹⁴

The direct source of copper for incorporation into Descemet's membrane is in dispute. It has been suggested¹⁵ that the limbal circulation could be the source, while others^{2,12} regard the aqueous, which contains elevated levels of copper,⁴ to be the source. We believe the case we have described provides strong circumstantial evidence for the latter theory. The limbal circulation of our patient's right eye had not been disturbed, whereas his aqueous production was greatly reduced as shown by the extremely low intraocular pressure. We presume therefore that there was a much lower through-put of copper in the aqueous of his right eye, so that a Kayser-Fleischer ring did not form in this eye.

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Unilateral Kayser-Fleischer ring

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SUMMARY A patient is presented who had unrecognised Wilson's disease. He had developed a clinically obvious Kayser-Fleischer ring in only one eye. The eye without the corneal ring had been injured in childhood and had a low intraocular pressure. Possible mechanisms for formation of a Kayser-Fleischer ring are reviewed and the lack of Kayser-Fleischer ring in this case is discussed.

Case history

The patient first noticed a slight tremor of his hand and slight unsteadiness of gait at the age of 35. These symptoms progressed very slowly, and he was first seen by a neurologist at the age of 52. Signs present at that time were unsteadiness, cerebellar dysarthria, and ataxia of the hands, the right more than the left. The right eye was blind and divergent, the result of a penetrating injury by a dart at the age of 7.

His past medical history revealed an episode of jaundice as a teenager and a urinary infection at the age of 40. Relevant family history was that his identical twin brother had died of hepatitis at the age of 47. He had also suffered from ataxia of a similar severity.

Heredofamilial ataxia was diagnosed.

The patient's condition gradually worsened until at

the age of 56 he was unable to walk without the aid of a stick. At the age of 60 he was admitted to hospital because of liver failure. He was jaundiced, had palmar erythema, spider naevi, and pigmentation. His liver was enlarged and he had ascites. He was anarthric and aggressive.

The eye findings were as follows: The right eye (Fig. 1) was divergent; there was a corneal scar which did not obscure iris detail. There was a dense cataract precluding a view of the fundus. The corneal periphery appeared normal, including the area at the limbus at 6 and 12 o'clock. The intraocular pressure was low, giving a measure of zero on the Goldmann applanation tonometer.

The left eye (Fig. 2) appeared healthy. The only abnormality was a brown ring 3 mm wide at the corneal periphery and extending around 360° of the circumference. The pigment lay at the level of Descemet's membrane and was diagnosed as a Kayser-Fleischer ring. Intraocular pressure was



Fig. 1 Divergent right eye with no evidence of Kayser-Fleischer ring. Left eye has a dense Kayser-Fleischer ring.

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(Snellen chart), one eye was illuminated for 30 s with a penlight held 2 to 3 cm from the eye. The PSRT was measured in seconds as the time required to read the Snellen letters on the line above that of best corrected visual acuity. Each eye was tested separately. Flutamide (Euflex) was supplied by Schering Canada Ltée, Montreal while Anandron was provided by Roussel Canada Ltée, Montreal.

Results

The detailed ophthalmological examination was suggested by the complaint of a delay in visual function following bright illumination in approximately 65% of patients who were receiving Anandron. This visual defect was particularly embarrassing during bright days, when vision could be delayed for several minutes when entering artificially illuminated surroundings. Exposure to the brightness of television screens was also sufficient to cause similar visual impairment in many patients. The ophthalmological examination showed no visual acuity worse than 6/21 in any subject. Slit-lamp examination, applanation tonometry, and fundus examination were within normal limits in all cases. As shown in Table 1, 12 of 18 patients (67%) showed an increase in the PSRT above the normal value of 80 s. The observed values ranged between 20 and 1500 s (25 min), with an average of 9 min. This delay in the PRST was observed as early as one month after

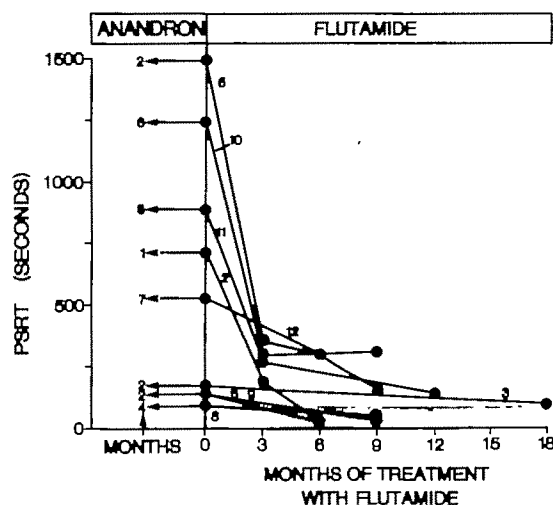


Fig. 1 Effect of changing from Anandron (RU) to flutamide on the photostress recovery time (PSRT). The right-hand numbers identify the patients in Table 1 while the left-hand numbers indicate the duration of treatment with Anandron (months).

initiation of treatment and remained present for as long as the drug was given. Six patients (33%) did not show a delay of PRST value.

Owing to the visual side effects Anandron was discontinued and replaced by flutamide in the nine patients having more severe subjective symptoms. In all cases the PSRT decreased markedly during the first time interval studied, namely three months. Some patients had been treated with Anandron for only one month, while others had received this drug for seven months. Patients who were most affected by Anandron and had a more prolonged PSRT did not show a complete recovery of the PRST value when changed to flutamide, even 12 months after discontinuation of Anandron. However, in all cases subjective symptoms disappeared within two to four weeks after changing from Anandron to flutamide.

Discussion

Compliance by the patient is a major problem which can seriously limit the efficient treatment of chronic diseases. This is especially true for the treatment of prostatic cancer, a disease affecting patients with an average age of 67 years and frequently suffering concurrent illnesses. Compliance in these patients can be easily compromised by any side effect of a drug, since it is most tempting to avoid taking the drug when the cancer is in remission and/or no pain or other symptom of the cancer is present. The consequences of a lack of compliance to the anti-

Table 1 Visual acuity and photostress recovery time in patients with prostatic cancer treated with the antiandrogen Anandron

Patient	Age (yr)	Prior treatment	Treatment duration (months)	Visual acuity*	PSRT (seconds)*
1	71	Orch	1	6/6	360
2	69	Orch	1	6/9	720
3	69	Orch	2	6/7.5	180
4	78	None	2	6/9	183
5	80	None	2	6/7.5	1500
6	56	None	2	6/6	150
7	71	None	4	6/21	420
8	75	Tace	4	6/12	100
9	65	Tace	5	6/9	150
10	74	None	6	6/6	1260
11	80	None	6	6/7.5	900
12	71	None	7	6/7.5	540
13	62	None	1	6/9	45
14	67	DES	3	6/6	58
15	63	DES	4	6/6	45
16	62	Orch	4	6/6	30
17	67	Orch	6	6/6	20
18	58	None	18	6/9	15

Orch=orchiectomy DES=diethylstilbestrol

Tace=chlorotriamene

*Results for one eye

Ocular toxicity of Anandron in patients treated for prostatic cancer

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SUMMARY Approximately 65% of patients with prostatic cancer treated by the combination therapy using a gonadorelin (LHRH) agonist or orchidectomy in association with the antiandrogen Anandron complained of a delay in recovering vision after bright illumination (sun, television, bright light). Detailed ophthalmological examination revealed an increase in the photostress recovery time to an average of 9 min, while the upper limit of normal is 1 min 20 s. When treatment was changed from Anandron to the other pure antiandrogen flutamide, the value of the photostress recovery time markedly decreased and the visual symptoms rapidly disappeared. Since uninterrupted administration of the antiandrogen is of the outmost importance for the successful therapy of prostatic cancer, the availability of a compound such as flutamide that has no side effect other than those due to hypoandrogenicity should greatly facilitate compliance by the patients and the success of the treatment.

Antiandrogens have recently been added as part of a combination therapy with gonadorelin (LHRH) agonists or orchidectomy for the treatment of advanced prostatic cancer.¹⁻³ This treatment is based on a more complete blockage of androgens of both testicular and adrenal origin: testicular androgens are eliminated by surgical castration or by chemical castration with an LHRH agonist, while simultaneously the action of the relatively high level of androgens of adrenal origin which remain in prostatic cancer tissue after castration is blocked in the prostatic cancer itself by a highly specific androgen antagonist or pure antiandrogen. When such complete blockage of androgens is achieved with the combination therapy, not only a greater percentage of patients show an objective response at the start of treatment but there is a much longer duration of the response and a marked improvement in survival.¹⁻³

The only side effects observed with this treatment are related to the complete inhibition of androgens: a decrease or loss of libido in 75% of patients and hot flushes in approximately 80% of cases. However, with one antiandrogen, namely Anandron, approximately 65% of patients complained of visual symp-

toms. The predominant visual side effect was a delay in recovering visual function after bright illumination (sun, television, bright light). This study provides an objective assessment of visual function in patients receiving the antiandrogen Anandron and the rapid recovery observed following change from Anandron to flutamide.

Patients and methods

Ophthalmic examinations were performed on 18 patients treated for prostatic cancer with the antiandrogen Anandron (5,5-dimethyl-3[4-nitro-3-trifluoromethyl]phenyl]-24-imidazolidinedione (RU23908) at the dosage of 100 mg every eight hours. This compound is an analogue of the pure antiandrogen flutamide (Euflex) (4'-nitro-3'-trifluoromethyl-isobutyranilide). Owing to the severity of the subjective symptoms nine out of 18 patients started on Anandron were changed to flutamide at the dosage of 250 mg every eight hours. The average age of the patients was 68.8 years.

The ophthalmic tests were corrected visual acuity, slit-lamp examination, Goldmann applanation tonometry, fundus colour photography, and photostress recovery time (PRST). This test was performed as follows: after measurement of corrected visual acuity

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Subretinal neovascularisation and snow banking in a case of sarcoidosis: case report*

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SUMMARY A 49-year-old Japanese man presented with chronic granulomatous uveitis in his left eye. Later he developed macular subretinal neovascularisation. The chest x-ray showed bilateral hilar lymphadenopathy. Bronchoscopy and gallium-67 scanning were positive, PPD skin test negative, and serum angiotensin converting enzyme (ACE) levels increased. Ophthalmoscopy and fluorescein angiography of the left eye showed perivasculitis, retinochoroidal exudates, snow banking, and vitreous opacity. On these findings, the diagnosis of sarcoidosis was made. Treatment was based on topical corticosteroids, mydriatics, beta blockers, and oral carbonic anhydrase inhibitors. After 15 months the visual acuity decreased in the left eye, and a neovascular membrane was observed in the macula. Fluorescein angiography confirmed subretinal neovascularisation. Almost two years later the patient still has the neovascular membrane in his left eye.

Sarcoidosis is a granulomatous systemic disease with various clinical features. Among them we can frequently find lesions of the lungs, skin, and eyes.¹ It may commonly present with chronic granulomatous anterior uveitis, vitreous opacities, retinal vasculitis, and chorioretinal involvement. But there have been few reports of retinal or subretinal neovascularisation² and pars planitis³ associated with sarcoidosis.

The purpose of this paper is to present two unusual findings—macular subretinal neovascularisation and snow banking—which were encountered in a patient with ocular sarcoidosis.

Case report

A 49-year-old man was referred to the Uveitis Survey Clinic of the Hokkaido University Hospital on 22 November 1982 because of decreased vision and floating spots in his left eye. He suffered from acute hepatitis in November 1981, but he had had no ocular disease before.

On initial ophthalmological examination his corrected visual acuity was 1.0 in the right eye and 0.4 in the left eye. Applanation tonometry showed 20 mmHg in the right eye and 22 mmHg in the left eye. The anterior chamber of the right eye was clear, with no flare and cells. In the left eye the anterior chamber showed 1+ flare and 3+ cells, with medium sized keratic precipitates on the corneal endothelium. The right eye was normal on ophthalmoscopic examination, and there was no sign of intraocular inflammation. The left eye showed 2+ vitreous opacities, cystoid macular oedema, perivasculitis, retinochoroidal exudates, and marked snow banking in the inferior periphery of the fundus. The optic disc was reddish, with clear margin (Fig. 1, 2).

Chest x-rays showed bilateral hilar lymphadenopathy (BHL); a skin test to 0.05 µg-0.1 ml of purified protein derivative of tubercle bacillus (PPD) was negative. Serological tests for syphilis were negative, serum complement activity was 43.9 CH50 units per ml, antinuclear antibody titre 10 units, and serum angiotensin converting enzyme (ACE) positive with 42 units per ml. Bronchoscopy showed reticular pattern, with new vessel formation, characteristic of sarcoidosis. Gallium-67 scanning disclosed increased uptake in the parotid, nasopharyngeal, and lung areas (Fig. 3). Based on these data, the diagnosis of sarcoidosis was established.

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*Part of this paper was presented by Dr Pellegrini at the 131st meeting of the Hokkaido Ophthalmological Society on 21 October 1984.

androgen therapy is the development of autonomous tumours which will be unresponsive to any further therapy at the time of relapse.¹⁴

Visual side effects should be carefully interpreted in elderly patients. Although increased PSRT with increasing age has been reported, the value for normal individuals is no higher than 80 s.^{5,8}

As performed, the PRST test evaluates the macular function, but it is independent of the visual acuity up to 6/24.⁸ Moreover, fundus ophthalmoscopy of the patients revealed no anatomical change of the retina. The PSRT measures the return of visual function after bleaching of the visual pigments of the photoreceptors. Therefore an increase in the PSRT value indicates a delay in regeneration of visual pigments. This can be the result of an alteration in the outer retinal segment, pigment epithelium, choriocapillaris, or the choroid. From indirect evidence it has been suggested that the photostress recovery time is dependent on the inner nuclear layer of the retina.⁹ This hypothesis is based on the observation that the modifications of the photostress recovery time follow those of the oscillatory potentials of the electroretinogram (ERG), which are known to originate from the inner nuclear layer.¹⁰ Despite the uncertainties about the pathophysiological basis of delayed vision, the photostress recovery time is a reliable measure of visual function, and it permits a quantitative assessment of the symptoms of delayed vision.

The present data show that approximately 65% of patients with prostatic cancer receiving Anandron as part of the combination therapy have an increase of the photostress recovery time, with values up to 25 min, the upper limit of normal being 1.2 min. Symptoms disappeared in all the patients when

Anandron was changed to flutamide, a pure anti-androgen having no such visual side effect. Since compliance is of the outmost importance in patients with prostatic cancer, the availability of an anti-androgen having no visual side effect, such as flutamide, is of great medical importance.

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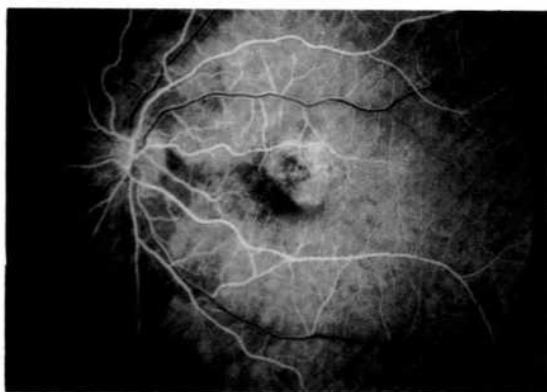


Fig. 4 Fluorescein angiography of the left eye showing leakage of the subretinal neovascularisation (reticular pattern) and slight leakage from the optic disc (25 seconds after injection).

head should be included in gallium citrate scans whenever the diagnosis of sarcoidosis is being considered, and stated that over four-fifths of the patients with active sarcoidosis showed increased uptake by the lacrimal glands. In our patient gallium-67 scanning disclosed increased uptake not only in the hilar areas of the lung but also in the parotid and nasopharyngeal areas. The PPD skin test, which was negative in this patient, was reported by Obenaus *et al.*⁵ to be negative in 95.7% of their cases. Angiotensin converting enzyme, increased in our patient, has been correlated with sarcoidosis by many authors.⁸⁻¹¹ Bronchoscopic findings have recently been shown to be rather important for the diagnosis of sarcoidosis. Kobayashi *et al.*¹² performed bronchoscopy in 130 patients with sarcoidosis and found that 88% had a network formation of small blood vessels (NFSBV) in the trachea and/or large bronchi

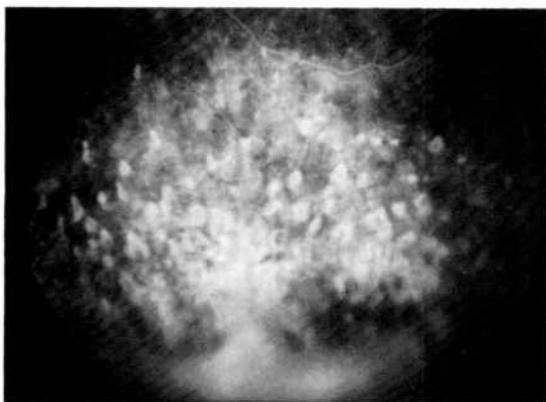


Fig. 5 Fluorescein angiography of the left eye, showing hyperfluorescence of the snow banking and retinochoroidal atrophic lesions (105.5 seconds after injection).

as compared with 4% of the controls. They concluded that these network formations were a characteristic finding in sarcoidosis.

Although Frank and Weiss⁴ have reported a well illustrated case, subretinal neovascularisation in sarcoidosis is rare. This rarity may be partly explained by the fact that some complications in chronic uveitis, such as posterior synechiae of the iris, complicating cataracts, or vitreous opacity, make it difficult to obtain a good fluorescein angiogram.¹³

The exact cause of the proliferation of choroidal vessels is unknown, and no satisfactory experimental model of choroidal neovascularisation has yet been found. Bruch's membrane seems to have an important role, acting as a mechanical barrier that may separate new choroidal vessels from the subpigment epithelial space, and, when it is ruptured, newly formed choroidal vessels will grow through the rents.¹⁴

Archer and Gardiner¹⁵ produced experimental choroidal neovascularisation in the rhesus monkey by photocoagulation and suggested that new choroidal vessels are formed by proliferating endothelial cells originating by mitosis in injured and exposed choroidal vessels at photocoagulation sites. Recently, however, Henkind¹⁶ stated that choroidal neovascularisation does not require breaks in Bruch's membrane, but rather that new vessels can literally dissolve the membrane. He considers that the retinal pigment epithelium produced a factor responsible for inducing the formation of new vessels from the choroid.

Photocoagulation has been proposed as the best means of treating choroidal neovascularisation.¹⁴ Nevertheless, Hoogstede and Copper¹³ suggested that remission of the subretinal neovascularisation may follow the use of systemic corticosteroids. In our case systemic corticosteroids were not given, because the patient lived far from the hospital and it was difficult to examine him regularly. On the other hand photocoagulation was not performed owing to the foveal localisation of the vasculature and the presence of a subretinal fibrovascular scar that made it difficult to delineate the exact extent of the nets, making photocoagulation a dangerous procedure. Snow banking, a common finding in pars planitis (intermediate uveitis), is rare in patients affected with sarcoidosis.³ In our experience¹⁷ in 95 patients (176 eyes) with ocular sarcoidosis 50 eyes (28.4%) had coarse vitreous opacities and 46 (26.1%) fine vitreous opacities, but none showed snow banking. But because of their importance in the course of the disease we recommend that subretinal neovascularisation and snow banking should always be carefully sought, as they may sometimes be encountered in association with ocular sarcoidosis.

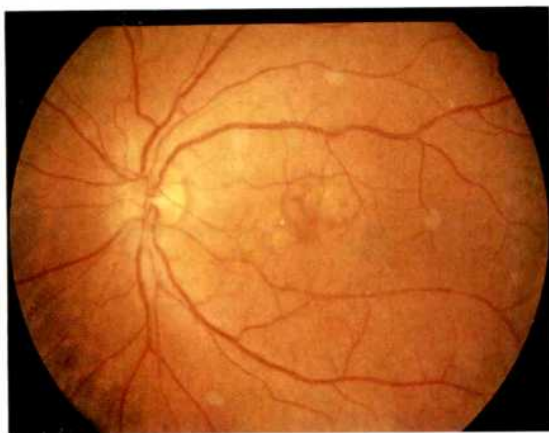


Fig. 1 Fundus picture (posterior pole) of the left eye showing depigmented area and subretinal neovascular membrane in the macula.

The patient was treated with topical corticosteroids, mydriatics, beta blocker agents, and oral carbonic anhydrase inhibitors. Inflammation of the anterior segment of the left eye was well controlled with topical treatment, but the cystoid macular oedema persisted. A posterior sub-Tenon's injection of 40 mg of methylprednisolone acetate was there-



Fig. 2 Fundus picture (inferior periphery) of the left eye showing marked snow banking, retinochoroidal atrophic lesions, and perivascular sheathing.

fore given in the left eye on 7 December 1982. The cystoid macular oedema gradually decreased, and during the following 15 months the patient's condition remained stationary, with visual acuity maintained at about 0.3 and with no clinical exacerbation.

In February 1984, however, he returned to our Uveitis Survey Clinic complaining of decreased vision in his left eye. The left visual acuity was 0.1, and ophthalmoscopic examination showed a neovascular membrane surrounded by a depigmented area in the macula. A small retinal haemorrhage was also detected. Fluorescein angiography showed in the early phase a reticular leakage pattern in the macula, which gradually increased in the late phase. The presence of subretinal neovascularisation was clearly shown in the left macula. No retinal avascular area was noted, but there was a slight leakage from the optic disc and tissue staining of some retinal vessels (Figs. 4, 5).

Six months later fluorescein angiography was performed again, and the same findings were obtained in the left eye.

Discussion

Although biopsy has not been performed, various laboratory findings gave us a definite clinical diagnosis of sarcoidosis in this case.

The bilateral hilar lymphadenopathy (BHL) in our case is a characteristic finding.^{4,5} Gallium-67 scanning, though the mechanism of the gallium uptake is obscure, is considered to be a sensitive method for detecting systemic as well as ophthalmic changes in sarcoidosis.⁶ Weinreb and Tessler⁷ reported it as being even more sensitive than chest roentgenograms. They also recommended that views of the



Fig. 3 Gallium-67 scanning disclosing increased uptake in the mediastinal and bilateral hilar areas.

Correspondence

Spectacle prescribing among 10-year-old children

SIR, Your editorial in the December issue of the *BJO* uses my paper¹ to draw inferences which the data published in it cannot support. The data do strongly suggest that over-prescribing of spectacles is common in children but provide no information on who was responsible for these prescriptions.

You imply that the cause is entirely prescribing by opticians to children with medical problems such as headaches. Although the latter were more common among children with questionable prescriptions, they were actually reported by less than 20%. Treatment of headaches is therefore an unlikely explanation for more than a small proportion of questionable prescriptions.

We do not know what proportion of children were treated by opticians and what proportion by doctors in eye clinics. Both of these groups see children and both could have been responsible for the observed overprescribing.

Department of Child Health, SARAH STEWART-BROWN
Royal Hospital for Sick Children,
65 St Michael's Hill,
Bristol BS2 8DZ

Reference

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**We agree with Dr Stewart-Brown that her paper gives no information as to who was responsible for the spectacle prescriptions. Our editorial note contains the phrase 'if we assume that the proportions conform to the national average, it would be likely that 80-90% of the prescriptions would have been issued by non-medically qualified persons.' Furthermore, we certainly do not assume that all the unnecessary prescriptions were given for headache, and we mention no less than seven other possibilities. However, we accept that a cursory reading of the editorial could give the impression that Dr Stewart-Brown's paper had pinpointed headache as the principal cause of the over-prescribing, and we hasten to agree with her that such was not necessarily the case.—EDITOR.

Defective vision in children

SIR, I read with interest the papers by R M Ingram and colleagues,^{1,2} which proved useful additions to the literature. However, the interpretations made in the second paper² with regard to the success of occlusion are somewhat narrow. It would seem that the results are said not to be encouraging because final acuity is not 6/6. Despite this assertion, the average improvement is virtually two Snellen lines and the maximum benefit five lines (using an interpre-

tation which takes the pessimistic view that an improvement from <6/60 to 6/60 is equivalent to a single line's improvement).

If it is accepted that there is an innate variation in visual capability among normals, that the Snellen chart is an irregularly progressive assessment of acuity, and that an improvement in acuity of only one line may be of visual significance in some cases, then I would submit that the results submitted are moderately encouraging. This evaluation of the results does not of course negate the argument that a better response might be achieved with screening and management before the end of the first year of life.

London Refraction Hospital,
56-62 Newington Causeway,
London SE1 6DR

K H EDWARDS,
Secretary

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SIR, Certainly there was some improvement in the acuity of children identified as having defective vision at 3½, but the real question is whether it was more than it would have been if they had not been identified until 5 years of age (under present arrangements for vision screening at school). Until this has been clearly demonstrated, there is no reason either to institute a new (additional) screening test or to change the present arrangements. Indeed it could be disadvantageous to do so.¹

Kettering and District General Hospital,
Rothwell Road,
Kettering NN16 8UZ

R M INGRAM

Reference

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Obituary

A. J. Boase, CMG, OBE, FRCS, LRCP, DOMS

Mr Arthur Joseph Boase, formerly ophthalmic surgeon in Uganda and later in Jerusalem, died peacefully on 31 January 1986 aged 84 years.

Arthur Boase was born in British Guiana, where his father was a medical officer. He was educated at Mount

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together in a large two-volume textbook on glaucoma which is due to be published in the next few months and will undoubtedly become a classic reference volume in the field of glaucoma.

John Cairns was a shrewd observer and a careful and original thinker. He was infinitely patient, kind, and gentle in dealing with his patients and a quite exceptionally lucid teacher both as a lecturer and as a teacher of surgical technique. He was a perfectionist not only in his work but also in his greatest hobby, gardening. He won the local horticultural challenge cup on no less than 17 successive occasions. Those who worked under him were expected to have similar high standards, but even if they were put on the carpet the interview would always be lightened with a joke or anecdote and always ended in laughter.

In the incredible courage with which he faced his last distressing illness and his ability to return to work he was greatly helped by Denise, his wife, and his two sons, Hugh and Neil, of whom he was so quietly proud. We have all lost a great man and a wonderful companion.

pgw

Notes

A new Eye

The *Transactions of the Ophthalmological Societies of the United Kingdom* will change its title to *Eye* from 1 January 1987.

IAPB Third General Assembly

The International Agency for the Prevention of Blindness (IAPB) Third General Assembly will convene in New Delhi, India, on 6-11 December 1986. The theme will be 'A decade of progress.' Persons wishing to attend should register before 1 July 1986 and send name, affiliation, address, telephone number, and registration fee (\$65.00) to IAPB President Carl Kupfer, MD, National Eye Institute (Code TG), Building 31, Room 6A03, Bethesda, Maryland 20892, USA.

St Mary's, the Jesuit College in Derbyshire, and at St Thomas's Hospital Medical School, where he graduated in medicine in 1923 at the early age of 22 years.

In 1924 he joined the Colonial Medical Service and was appointed to Uganda, where in 1929 he married Alice, daughter of Sir Charles Griffin, QC. Five sons and five daughters were the product of this long and happy marriage. Early in his career he specialised in ophthalmology, though this had to be combined with the duties of a general medical officer until 1945, when he was finally gazetted as senior specialist ophthalmologist. In addition to his clinical duties, Arthur Boase was at various times president of the East African Association of Surgeons and the Uganda branch of the BMA. Together with his colleagues he was instrumental in founding the medical school at Makerere. He was also the first chairman of public health when Kampala became a municipality. Despite these many commitments Arthur Boase found time to be an enthusiastic golfer and to develop an interest in woodwork, which was to be his absorbing hobby well into his retirement.

Arthur Boase retired from Uganda in 1956 to take up the post of warden of the Ophthalmic Hospital of the Order of St John in Jerusalem. The next 13 years proved to be very eventful. The early days were spent in the cramped quarters of Watson House in the old City before moving to the large modern Eye Hospital which was built on the northern outskirts of Jerusalem. During this time the hospital acquired a remarkable reputation throughout the Middle East, and every year record numbers of patients were treated. A visit to the Eye Hospital was an important part of the itinerary of many pilgrims visiting the Holy City. Under Arthur Boase's wardenship the hospital became a popular place for ophthalmic surgeons from Britain and America to round off their training. The years spent in Jerusalem also had their dangerous moments; anti-British sentiment necessitated evacuation during the Suez campaign, and later he and his wife were caught up in the middle of the Six Day War. He was regarded with affection and esteem by the Jordanian people.

On retirement from Jerusalem in 1969 he went to live in Uckfield, Sussex. However, his professional services were still needed and he continued to work part-time until he was 76 years old.

During his long and distinguished career Arthur Boase was awarded, in addition to his other honours, the KStG and the KStJ. He is survived by his wife and eight of his 10 children, one of whom is a consultant ophthalmologist.

John Edward Cairns, MA, MB, BS, FRCS

In the loss of John Cairns British ophthalmology has been deprived not only of one of its most able and well known ophthalmologists but one of its most likeable characters. John, born in 1925 of farming stock, was brought up in the countryside of Northumberland, where he acquired the most acute powers of observation, his unusual and delightful sense of humour, an intense interest in all natural phenomena, and the most extraordinary accuracy with a catapult.



John Edward Cairns.

He was educated in King Edward VII Grammar School in Morpeth and then went to Durham University to read classics until he was called in up in 1943. He joined the Indian Army in which he was commissioned and remained until 1947. Although he never returned to India, his knowledge of the mountains, its wild life, particularly its entomology, and its people was encyclopaedic. He had intended on his return from the Army to become a schoolmaster; fortunately he decided instead to enter St Bartholomew's Hospital Medical School. He took the anatomy prize in the second MB and after qualification was house officer on both professorial units. It was then that Henry Stallard interested him in eye surgery, and after working with him John subsequently completed his eye training at Moorfields Eye Hospital, City Road, London. He worked for a time in London until he was appointed to Addenbrooke's Hospital, Cambridge, in 1964.

When he arrived in Cambridge the work load was enormous. He tackled this with his characteristic energy, deciding on priorities and then ensuring that they were carried out. All this was achieved apparently effortlessly and with a gentle humour. As the department began to come together he developed his abiding interest in glaucoma surgery, first in the development of that operation for which he will always be remembered, trabeculectomy, and later in modifications of iridectomy and latterly internal trabecular surgery. All of this interest has been brought

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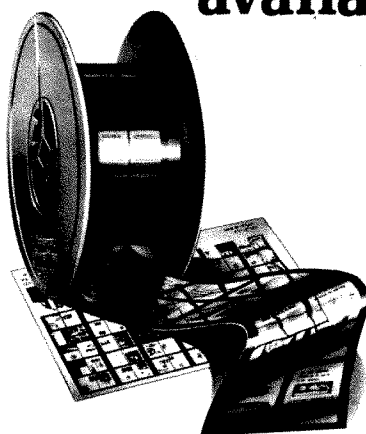
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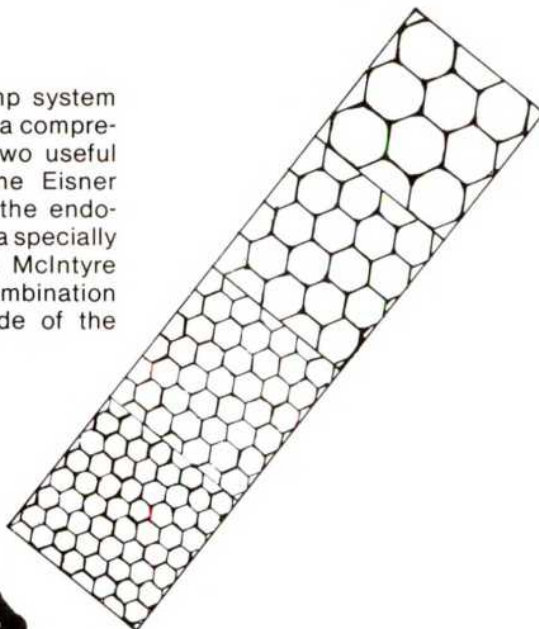
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